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NATIONAL RESEARCH COUNCIL OF CANADA
ASSOCIATE COMMITTEE ON SCIENTIFIC CRITERIA
FOR ENVIRONMENTAL QUALITY

2,4-D: SOME CURRENT ISSUES

Subcommittee on Pesticides and
Industrial Organic Chemicals

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The Associate Committee on Scientific Criteria for Environmental Quality was established by the National Research Council of Canada in response to a mandate provided by the Federal Government to develop scientific guidelines for defining the quality of the environment. The concern of the NRCC Associate Committee is strictly with scientific criteria. Pollution standards and objectives are the responsibility of the regulatory authorities and are set for the purpose of pollution control. These may be based on scientific criteria as a starting point but they also take into account the optimal socioeconomic impact of proposed measures as well as the state of existing technology.

The Associate Committee's program includes the evaluation of available information on the probability of effects of contaminants on receptors together with the related fundamental principles and scientific knowledge. In this work particular attention is directed to receptors and contaminants (and their interactions) important to Canada. This Canadian approach is necessary because evaluations made in other countries or regions will not always be applicable to the particular circumstances prevailing in Canada.

Members of the Associate Committee, its Subcommittees and Expert Panels, serve voluntarily and are selected for their individual competence and relevant experience with due consideration for a balance among all sectors in Canada. Responsibility for the quality of study documents rests with the Associate Committee. Each report is carefully reviewed according to a multistage procedure established and monitored by the National Research Council of Canada in order to preserve objectivity in presentation of the scientific knowledge. Publication and distribution of the report are undertaken only after completion of this review process.

Comments on Associate Committee documents are welcome and will be carefully reviewed by the Expert Panels. It is foreseen that these scientific criteria may be revised from time to time, as new knowledge becomes available.

All documents published by the Associate Committee are published in both French and English.

TERMS OF REFERENCE OF THE SUBCOMMITTEE ON
PESTICIDES AND INDUSTRIAL ORGANIC CHEMICALS

- (1) The preparation of reports critically evaluating and collating the available cause-effect relationships which permit the estimation of the environmental risks associated with the use of synthetic organic chemicals in Canada - these documents will provide criteria for the evaluation of both present and future use patterns, and
- (2) the identification of gaps in available criteria and preparation of recommendations for future research in these areas.

To meet this mandate, the Subcommittee has identified a number of priority compounds for consideration. Comprehensive reports are prepared to bring into perspective the diverse and somewhat obscure observations found in the literature. The documents consist of reviews, summarizing the available criteria and the research required. They also contain as supporting material the available data on which the overview is based.

The mandate of the Subcommittee does not include the setting of objectives and standards, the development of risk assessment, or the establishment of registered uses for pesticides in Canada. Therefore, it does not permit consideration of the engineering, economic, or legal aspects. The Subcommittee is only concerned with scientific information and environmental criteria. The documents do provide one of the components necessary in the consideration and development of risk assessments. Other agencies, both federal and provincial, have the actual responsibility for making decisions about the uses of specific synthetic organic chemicals in Canada and hence they have the task of bringing about an acceptable balance between the risks and benefits associated with the use of such chemicals by our society.

Inquiries concerning the activities of the Subcommittee should be directed to the Environmental Secretariat of the National Research Council of Canada, Ottawa, Canada.

NOTICE ON SUBCOMMITTEE MONOGRAPHS
CONTAINING INDUSTRIAL BIOTEST MATERIAL

Picloram: The Effects of Its Use as a Herbicide on Environmental Quality. 1974. NRCC No. 13684

Endosulfan: Its Effects on Environmental Quality. 1975. NRCC No. 14098

Fenitrothion: The Effects of Its Use on Environmental Quality and Its Chemistry. 1975. NRCC No. 14104

Fenitrothion: The Long Term Effects of Its Use in Forest Ecosystems - Current Status. 1977. NRCC No. 15389

Proceedings of a Symposium on Fenitrothion: The Long-Term Effects of Its Use in Forest Ecosystems. 1977. NRCC No. 16073

Bacillus thuringiensis: Its Effects on Environmental Quality. 1976. NRCC No. 15385

Polychlorinated Biphenyls: Biological Criteria for an Assessment of Their Effects on Environmental Quality. 1978. NRCC No. 16077

Ecotoxicology of Chlorpyrifos. 1978. NRCC No. 16079

Carbofuran: Criteria for Interpreting the Effects of Its Use on Environmental Quality. 1979. NRCC No. 16740

Approximately four years ago, it was recognized by Canadian and U.S. authorities that irregularities existed in some reports of animal studies carried out by Industrial Biotest Laboratories Incorporated of Northbrook, Illinois. A cooperative effort of Health and Welfare Canada and the U.S. Environmental Protection Agency to validate the studies indicates that safety evaluations of 97 pesticides are supported wholly or in part by studies from this contract laboratory. Audits of the individual studies indicate that a significant portion are invalid. These agencies have requested new studies when information central to the assessment of human safety is "suspect". Specific details of the concerns that form the basis of these requests are unavailable.

The following monographs of the NRC's Subcommittee for Pesticides and Industrial Organic Chemicals are affected: picloram, endosulfan, fenitrothion, Bacillus thuringiensis, polychlorinated biphenyls, chlorpyrifos and carbofuran. These documents contain some toxicological studies conducted by IBT which must be considered as "suspect" in light of the present situation. Hence, until the matter of the validation has been clarified, particular caution should be maintained to avoid the use of criteria developed on the basis of the IBT material. As additional information on the situation and replacement studies become available, the Subcommittee intends to review the need for updates of individual monographs.

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1.0 INTRODUCTION, CRITIQUE AND RECOMMENDATIONS

1.1 INTRODUCTION

As people have become more aware of and concerned with the quality of their environment, there has been an increase in public concern over the use of pesticides in general, and of 2,4-dichlorophenoxyacetic acid (2,4-D) in particular. 2,4-D, the major phenoxy herbicide in use in Canada, is used to control broad-leaved weeds and seedlings in agriculture (farm crops, rangeland and tree plantations), public parks and on private lawns. It is also used to maintain highways and electrical, communication, and pipeline rights-of-way. Because of its widespread use and its possible contamination with dioxins (especially the popular misconception that it is contaminated with 2,3,7,8- T_4 CDD^α, the most toxic dioxin), it is a much-publicized pesticide.

Extensive reviews of the environmental and human health criteria for 2,4-D exist (FAO/WHO 1971, 1972; NRCC 1978; US EPA 1982). Based on an examination of these reviews and of current public concerns (e.g. Warnock and Lewis 1978), four issues have been identified which, in our opinion, are particularly important for the assessment of the adverse effects of 2,4-D use in Canada.

The first two issues concern the toxicology of 2,4-D. One is the possible connection between the reproductive effects observed in laboratory animals treated with relatively high doses of 2,4-D and the presence of chlorinated dioxins as contaminants in the test formulations of 2,4-D. The limited data on the nature of the dioxins in 2,4-D and another phenoxy herbicide, 2-methyl-4-chlorophenoxyacetic acid (MCPA), show that while they do not contain the highly teratogenic 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, they do contain much less toxic dioxins. It is conceivable that the herbicides themselves are teratogenic (NRCC 1978). Because 2,4-D is so commonly used on private lawns and public areas, the question of whether exposure to the present formulations of 2,4-D (with lowered dioxin content) can cause reproductive effects is of particular public concern.

The second toxicological issue to be addressed is that of the neurotoxic properties of 2,4-D. A number of cases of peripheral polyneuropathy involving muscle and nerve damage have been reported in agricultural workers exposed to 2,4-D. Persons applying 2,4-D are the main identified group although effects on the nervous system have also been reported in workers involved in manufacturing 2,4-D in the Soviet Union.

^α 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

The third issue concerns the extent of the exposure encountered both by persons close to the application site and by those some distance away. This issue was chosen on the basis of recommendations in NRCC (1978): (1) that information be compiled on the levels of exposure encountered by field workers during spraying and (2) that studies be initiated to determine the drift of phenoxy herbicides. In the present analysis, a computer model is used to calculate bystander exposure from the aerial application of 2,4-D. Two situations representative of 2,4-D use in Canada were chosen: one on the Prairies and one in New Brunswick.

The fourth issue identified is the question of the association between phenoxy herbicides and disease observed in man. Several epidemiological studies have been published claiming an association between various cancers and phenoxy herbicide exposure. This has led to major public debate on the implications of these claims for Canadians.

1.2

CRITIQUE AND RECOMMENDATIONS

ISSUE 1: What is the connection between adverse reproductive effects and the dioxin contaminants in 2,4-D? (See Chapter 2 for details and references)

The herbicide 2,4-D has been reported to cause adverse reproductive effects in rats at doses of $50 \text{ mg.kg-BW}^{-1}.\text{d}^{-1}$ or above. It has also been reported to be a weak mutagen. Because of the highly toxic nature of the dioxin 2,3,7,8- T_4CDD found in 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) (another phenoxy herbicide) and the publicity it has been given, dioxins in 2,4-D formulations have been suspected as the cause of these birth effects. However, 2,3,7,8- T_4CDD has not been found in 2,4-D at the detection limit reported by Agriculture Canada ($1 \text{ }\mu\text{g.kg}^{-1}$). The presence of three other chlorinated dioxin isomers has been confirmed, namely 2,7-dichloro-, 1,3,7-trichloro- and 1,3,6,8- or 1,3,7,9-tetrachlorodibenzo- ρ -dioxins. Based on structure-activity relationships, these dioxins would be expected to be much less toxic than 2,3,7,8- T_4CDD . Only one of these isomers, 2,7-dichlorodibenzo- ρ -dioxin, has actually been tested for its potential to cause adverse reproductive effects; none were observed in rats at doses up to $2 \text{ mg.kg-BW}^{-1}.\text{d}^{-1}$. By comparison, the highest no-effect level documented for 2,3,7,8- T_4CDD in rats is $0.125 \text{ }\mu\text{g.kg-BW}^{-1}.\text{d}^{-1}$ ($\approx 16\ 000$ times less than that for 2,7- D_2CDD).

Examination of the limited information on the level of specific dioxin congeners in the various formulated products of 2,4-D, as well as their toxicity, does not support the suspicions that the dioxins are the causative agent. Unfortunately, the strength of any analysis is tempered by the lack of information on the dioxin content of the 2,4-D formulations used in the reproductive studies. In order to clarify whether 2,4-D formulations themselves are responsible for these effects, it is recommended that:

1. THE INFLUENCE OF THE DIOXIN CONTAMINANTS ON THE TOXICITY OF THE FORMULATED PRODUCTS SHOULD BE DETERMINED THROUGH REPRODUCTIVE STUDIES USING 2,4-D SAMPLES THAT CONTAIN A TYPICAL RATIO OF DIOXIN ISOMERS AT A SERIES OF DEFINED LEVELS. THESE LEVELS SHOULD INCLUDE THOSE FOUND IN TODAY'S FORMULATIONS AND OLDER FORMULATIONS.

ISSUE 2: What is the explanation for the neurological complaints seen in workers exposed to 2,4-D? (See Chapter 3 for details and references)

Neurotoxic effects have been observed in laboratory animals treated with 2,4-D and such effects are also reported to occur in agricultural and industrial workers. Although these reports suggest that the central nervous system is a target for 2,4-D, distribution studies at low doses report only low levels of 2,4-D in the brain. Several theories have been proposed to explain this dichotomy. It can be suggested that at very high doses, there is a sharply increased rate of influx of 2,4-D or associated metabolite(s) into the brain or other target sites. Studies administering ^{14}C -2,4-D and another phenoxy herbicide, ^{14}C -MCPA, to rats indicate that the distribution pattern of unbound labelled material was dose-dependent and was mediated by the extent of protein binding outside the brain. The labelled material has been assumed, but not proven, to be the unchanged parent compound. From in vitro studies and our calculations it appears that at relatively high doses (i.e. within 8-fold of the LD_{50}), as protein binding sites become saturated, increased levels of unbound 2,4-D are available to cross membranes such as the blood-brain barrier. Hence, in this situation, relatively more unbound 2,4-D is available at target sites.

The theory would be consistent with the neurological complaints expressed by workers exposed to acute high doses of 2,4-D although it would not explain complaints by workers exposed to chronic low doses. Conceivably, the use of solvents, emulsifiers and other chemicals in conjunction with 2,4-D could confound the issue. Solvents are known to cause effects on the central nervous system similar to those seen in association with 2,4-D. Based on this tentative explanation for the association between neurotoxicity and 2,4-D, we recommend:

2. AN EXAMINATION OF THE PHARMACOKINETICS, PARTICULARLY THE TISSUE DISTRIBUTION, BIOTRANSFORMATION AND DOSE-RESPONSE RELATIONS, FOR 2,4-D (NOT ONLY THE RADIOLABEL) WHEN ADMINISTERED AT VARIOUS DOSES.
3. THAT THE SOLVENTS AND EMULSIFIERS USED IN CONJUNCTION WITH 2,4-D BE TESTED FOR THEIR POTENTIAL TO CAUSE NEUROTOXIC EFFECTS.

ISSUE 3: What is the exposure to bystanders from the aerial application of 2,4-D? (See Chapter 4 for details and references)

The critical exposure groups for 2,4-D include women of child-bearing age; children who play on lawns and in public parks sprayed with 2,4-D; and bystanders (including applicators) near large scale spraying operations. Since there are no studies which directly examine the exposure of women or children in such situations, we have concentrated on the exposure to bystanders associated with aerial applications.

A computer model simulating the aerial spraying of 2,4-D formulations on both the Prairies and in New Brunswick was used to assess bystander exposure. The major exposure factors examined in the model were: the exposure route, the application techniques, the meteorological conditions and the extent of drift.

In agreement with general experience (Wolfe et al. 1972), the highest exposure was predicted to be via the dermal route. Exposure estimations from all routes were about two orders of magnitude higher in the New Brunswick situation than in the Prairies. This is due to the different nozzles used.

Of the two wind speeds modelled in the Prairie scenario, the estimated exposure was greater at the higher wind speed. This effect diminished with increasing distance from the spray line. Taking into account all of the above factors, at 800 m from the spray line and a wind speed of 1.5 m.s^{-1} , the total predicted bystander exposure was $9 \times 10^{-8} \text{ mg.kg-BW}^{-1}$ and $1 \times 10^{-5} \text{ mg.kg-BW}^{-1}$ for the Prairie and New Brunswick scenarios respectively (assuming 100% dermal absorption, which is a 20- to 50-fold overestimation).

When the results of the computer model were compared with field data for the exposure of observers at 20-150 m from the sprayline, they were of the same order of magnitude.

The computer-model predicted exposure estimates and drift potential of 2,4-D formulations used in New Brunswick are much lower than those predicted by the same model for aminocarb, a typical forest insecticide (NRCC 1982) (Table 1-1), even taking into account the much higher application rate of 2,4-D. This appears to be due to (1) less drift with herbicide spraying because the aircraft fly at much lower heights and (2) different droplet-size distributions. Absolute comparisons between herbicide and insecticide exposures are very difficult because of differences in application techniques, spray sites and formulation types. The exposure estimates provide an indication of the relative exposure associated with various spray programs.

Based on our present limited understanding of exposure and on the above analysis, we recommend that:

Table 1-1. Estimated total exposure^α to bystanders from the aerial application of 2,4-D^β and aminocarb.

Scenario	Wind speed (m.s ⁻¹)	Total Exposure ^γ (mg.kg-BW ⁻¹)
2,4-D (Prairie scenario)	1.5	$1.96 \times 10^{-10} \times X^{\delta}$
2,4-D (New Brunswick scenario)	1.5	$1.43 \times 10^{-8} \times X$
Aminocarb (NRCC 1982)	1.0	$4.0 \times 10^{-6} \times X$

^α Exposure is calculated at 400 m from the spray line.

^β The exposure calculation for 2,4-D is more precise because of the sophistication of the model.

^γ Uncorrected for dermal absorption.

^δ X is the application rate in g-AI.ha⁻¹.

4. ADDITIONAL FIELD STUDIES BE CONDUCTED TO VALIDATE THE COMPUTER MODEL ESTIMATIONS OF EXPOSURE TO 2,4-D FORMULATIONS.
5. APPLICATION TECHNIQUES (e.g. NOZZLE TYPE) BE CHOSEN TO MINIMIZE EXPOSURE. STANDARD NOZZLES SHOULD BE CHOSEN ON THE BASIS OF EXISTING DATA AND A DESIRABLE DROPLET DISTRIBUTION RANGE. THE TOTAL DELIVERY SYSTEM AND DRIFT REDUCTION ADDITIVES SHOULD ALSO BE INVESTIGATED. THIS APPLIES FOR ALL HERBICIDES, FUNGICIDES AND INSECTICIDES.
6. ROUTINE EXPOSURE MONITORING OF WORKERS INVOLVED WITH SPRAYING BE CONDUCTED AND EXAMINED FOR CORRELATION WITH POSSIBLE ASSOCIATED HEALTH EFFECTS.
7. APPROPRIATE EXPOSURE STUDIES BE CONDUCTED ON PEOPLE USING SPRAYED PARKS AND SPRAYING PRIVATE LAWNS. (INCREASINGLY, THERE IS PUBLIC DEMAND FOR PRECAUTIONARY MEASURES, DURING AND AFTER SPRAYING, TO MINIMIZE POSSIBLE RISKS).

ISSUE 4: What is the strength of the association between phenoxy herbicides and disease? (See Chapter 5 for details and references)

The epidemiological literature for phenoxy herbicides is better developed than it is for most other pesticides. There have been several reports of an association between agricultural workers exposed to phenoxy herbicides and various cancers, particularly a rare type of soft-tissue sarcoma. Malignant lymphoma, stomach cancer and lung cancer are also reportedly associated. Owing to the large number of confounding factors, there is no unequivocal evidence that 2,4-D is the cause of these effects. Study subjects exposed to 2,4-D were usually also exposed to other phenoxy acids or chlorophenols, which may be contaminated with toxic dibenzodioxins, as well as other chemicals. The identification of an association is also difficult because of the different formulations of 2,4-D used, each with its own combination of solvents, emulsifiers and contaminants.

Based on our knowledge of the associations already reported between 2,4-D and health effects and the inherent difficulties in epidemiological studies, it is recommended that:

8. AN EPIDEMIOLOGICAL STUDY ON WORKERS EXPOSED TO "ONLY 2,4-D" BE CONDUCTED. WHILE SUCH A GROUP MAY NOT BE EASILY IDENTIFIABLE, THE RESOLUTION OF THIS ISSUE IS IMPORTANT AND SCIENTISTS AND ADMINISTRATORS SHOULD ALWAYS BE ALERT FOR SUCH A GROUP.

Adverse reproductive effects have also been discussed in association with the use of phenoxy herbicides, particularly with

respect to Agent Orange (a 50:50 combination of 2,4,5-T and 2,4-D) although no clear evidence has been found. Since dose-related reproductive effects have been demonstrated in laboratory animals, it is recommended that:

9. REPRODUCTIVE EFFECTS AS WELL AS CANCER INDICATIONS BE EXAMINED IN EPIDEMIOLOGICAL STUDIES. THE SHORT LATENCY PERIOD FOR REPRODUCTIVE EFFECTS WOULD ALLOW THEM TO BE STUDIED WITH LESS DIFFICULTY.

2.0 ISSUE: WHAT IS THE CONNECTION BETWEEN ADVERSE REPRODUCTIVE EFFECTS AND DIOXIN CONTAMINANTS IN 2,4-D?

The ability of chemicals to harm the embryo or fetus via maternal exposure is a controversial subject partly because of a lack of standard classification for such reproductive effects as fetotoxicity and teratogenicity, and because these effects are often interrelated. For the purpose of this document, fetotoxicity is defined as fetal mortality and morbidity (including resorption, reduced fetal body or organ weight, biochemical changes, etc.). Teratogenicity refers to permanent structural deformations or malformations observed in the embryo or fetus, e.g. skeletal anomalies, cleft palate or fused ribs. Other reproductive effects would include reduced fertility resulting from exposure of the male parent to a toxicant, or fetal abnormalities resulting from trauma during birth.

Chlorinated phenoxy herbicides are among the many groups of chemicals that are reportedly linked to adverse reproductive effects. This may be because these herbicides are frequently contaminated with chlorinated dioxins and furans. Of the 75 chlorinated dibenzodioxins, 2,3,7,8-tetrachlorodibenzo-p-dioxin is the most toxic and has been shown to be fetotoxic (Sparschu et al. 1971) and teratogenic (Courtney and Moore 1971); 2,3,7,8-T₄CDD occurs in some phenoxy herbicides, e.g. 2,4,5-T, as a contaminant (Esposito et al. 1980).

Because of differences in manufacturing processes, 2,4-D^α (unlike 2,4,5-T) is not expected to contain detectable levels of 2,3,7,8-T₄CDD, although it may be contaminated with other dioxin congeners. Cochrane et al. (1981) identified 2,7-dichloro-, 1,3,7-trichloro-, and 1,3,6,8- or 1,3,7,9-tetrachlorodibenzo-p-dioxins (Table 2-1) in samples of 2,4-D formulations. No other dioxin isomers were detected at the detection limit of 1 µg.kg⁻¹. Samples analyzed in Canada were selected from a variety of sources and were representative of the 2,4-D formulations available commercially in this country (Cochrane 1981). Because of the gross structural similarity of the 2,4-D-related dioxins to 2,3,7,8-T₄CDD, it has been speculated that the dioxins found in 2,4-D might cause adverse reproductive effects. The studies of Cochrane et al. (1982) suggest that the 2,4-D esters contain greater concentrations of chlorodioxins than does the 2,4-D acid.

Although the dioxin contaminants in 2,4-D have been positively identified, there is little information on their biological effects because most studies on the toxicology of dibenzodioxins have been

^α Besides the free acid, there are various forms of 2,4-D, including the sodium and amine salts and the isopropyl, isooctyl and butyl esters. Unless specified, the term 2,4-D is used here to denote any of these forms. It should be noted that 2,4-D esters are readily hydrolyzed to the free acid in the mammalian body (Erne 1966b).

Table 2-1. Concentration of dioxin contaminants in 2,4-D formulations (after Cochrane et al. 1981).

		Chlorinated dibenzodioxin concentration ^α (μg.kg ⁻¹)		
2,4-D	Number of Samples	2,7-D ₂ CDD	1,3,7-T ₃ CDD	1,3,6,8- or 1,3,7,9-T ₄ CDD
Esters				
Isooctyl	10	1814 ± 857	1152 ± 253	1398 ± 828
Butyl	7	4617 ± 3351	261 ± 89	184 ± 42
Acid	10	ND ^β	ND	ND
Amines	26	45 ± 22	118 ± 42	44 ± 16

^α Concentrations are in $\mu\text{g.kg}^{-1}$ (mean $\pm$ SE) based on 2,4-D acid (% w/w). Samples were obtained and analyzed by Agriculture Canada before the registration requirement in late 1981 that all 2,4-D products must contain less than 10 $\mu\text{g.g}^{-1}$ of total dioxins.

^β ND = not detected; limit of detectability was 1 $\mu\text{g.kg}^{-1}$.

devoted to the 2,3,7,8- T_4 CDD congener. Of the three dioxins identified in 2,4-D, only one has been tested directly for adverse reproductive effects. Schwetz et al. (1973) found that 2,7- D_2 CDD, administered at 100 mg.kg-BW⁻¹.d⁻¹, had no detectable adverse effects on the fetuses of Sprague-Dawley rats. There was a similar lack of detectable effects in Wistar rats treated with 2,7- D_2 CDD at 2 mg.kg-BW⁻¹.d⁻¹ (Khera and Ruddick 1973). Courtney (1976) did not observe any effects in CD-1 mice treated orally with up to 1 mg.kg-BW⁻¹.d⁻¹ of 2,7- D_2 CDD.

Toxicological evaluations of the other two dioxins do not exist and only speculative conclusions can be drawn. McConnell et al. (1978) found that while 2,3,7,8- T_4 CDD is the most toxic (LD₅₀ in mice = 284 µg.kg-BW⁻¹; LD₅₀ in guinea pigs = 2 µg.kg-BW⁻¹) congener tested, the toxicities of other congeners are 1000 to 10 000-fold lower. The toxicity of the congeners apparently varies with the number of chlorine atoms in lateral ring positions and other structural factors. Based on such structural considerations, the dioxins found in 2,4-D formulations are predicted to be much less toxic than 2,3,7,8- T_4 CDD.

Although 2,4-D has been reported to be fetotoxic and teratogenic (by the definition in this document) to rats at doses of 50 mg.kg-BW⁻¹.d⁻¹ when administered to pregnant rats on days 6-15 of gestation (Schwetz et al. 1971), none of these effects interfered with fetal or neonatal development, or survival. Fetotoxic and teratogenic effects have also been reported in hamsters at doses of 20-100 mg-2,4-D.kg-BW⁻¹.d⁻¹ administered to female hamsters on days 6-10 of pregnancy (Collins and Williams 1971).

Khera and McKinley (1972) reported that doses at or above 100 mg.kg-BW⁻¹.d⁻¹ of 2,4-D acid were fetotoxic (increased fetal mortality and decreased fetal weight) when administered to pregnant Wistar rats on days 6-15 of gestation (Figure 2-1). There was a nonstatistically significant fetotoxic effect at 50 mg.kg-BW⁻¹.d⁻¹. Doses at or above 25 mg.kg-BW⁻¹.d⁻¹ were found to be teratogenic (increased skeletal malformations) in the same experiment. These effects were only dose-related above 50 mg.kg-BW⁻¹.d⁻¹. Although the levels of dioxin contaminants in the formulations used in this study are unknown, if one assumes that the levels of di-, tri- and tetrachloro- homologs in these 2,4-D acid materials are similar to the detection limit used by Cochrane et al. (1981), the treatment of 50 mg.kg-BW⁻¹ would result in a daily dose of dioxins of about 0.15 ng.kg-BW⁻¹^α. The no-effect dose for effects on reproduction by 2,3,7,8- T_4 CDD in Wistar rats has been determined to be 0.125 µg.kg-BW⁻¹.d⁻¹ (Khera and Ruddick 1973). Thus,

^α If the dose of 2,4-D acid is 50 mg.kg-BW⁻¹ and the level of the three dioxin contaminants is the maximum, 3 µg.kg⁻¹, based on the limits of detectability (Table 2-1), then 50 mg.kg-BW⁻¹ x 3 µg.kg⁻¹ = 0.15 ng.kg-BW⁻¹ dioxin.

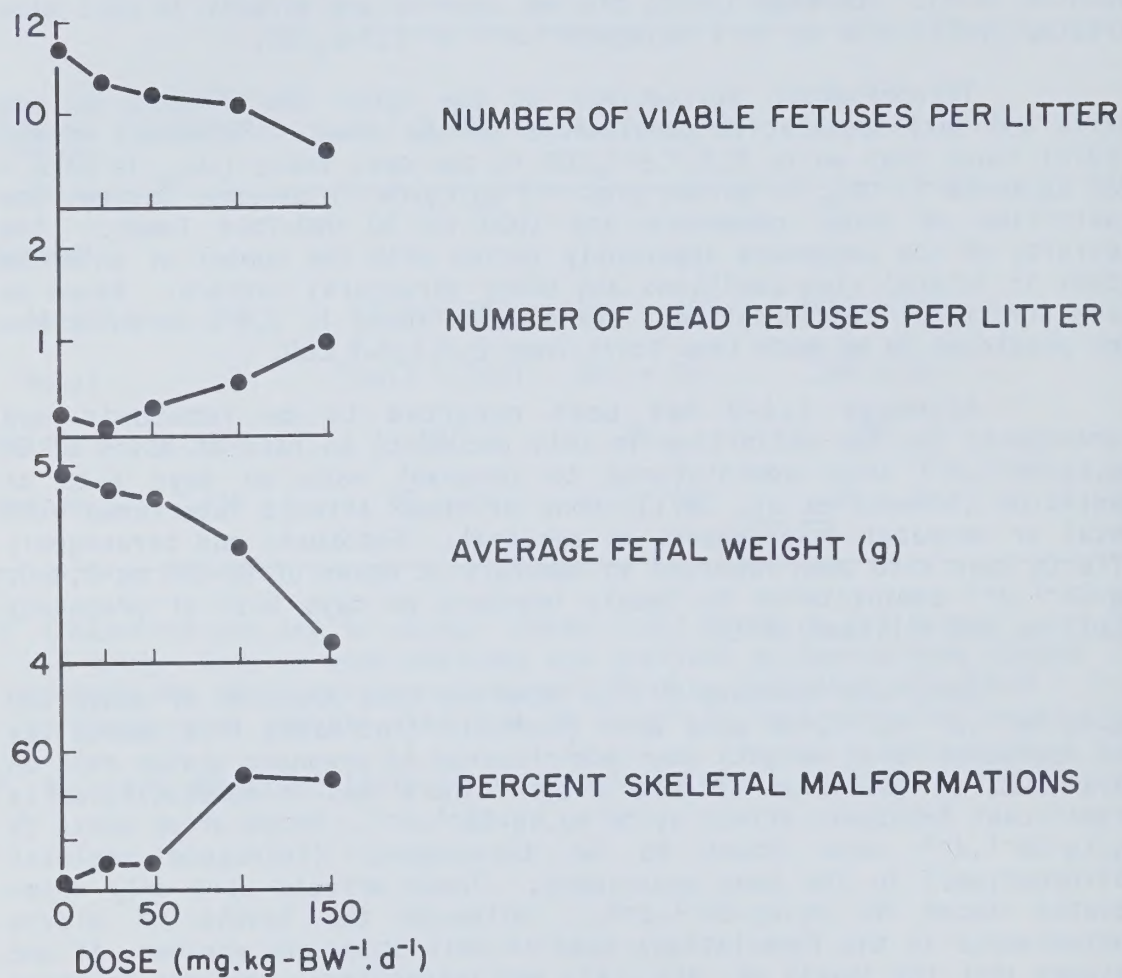


Figure 2-1. Averaged prenatal parameters following maternal treatment with 2,4-D acid in Wistar rats during days 6-15 of gestation (Khera and McKinley 1972).

even disregarding the differences in toxicity between 2,3,7,8- T_4 CDD and 2,4-D associated dioxins, the predicted dosage of the dioxins appears to be well below the no-effect level (830-fold) observed in this study. It should be noted that the level of dioxins now "permitted" is much less than it was several years ago.

Furthermore, the evidence suggests that the occurrence of these adverse reproductive effects may not be dose-related to the levels of dioxin contaminants in 2,4-D formulations. It has been mentioned that various 2,4-D derivatives contain different levels of dioxins (see Table 2-1). If these dioxins are connected with the observed effects, then the various 2,4-D derivatives at equivalent dosages would be expected to elicit an effect corresponding to their assumed dioxin content. The expected pattern was clearly not observed in the study of Khera and McKinley (1972) (Table 2-2).

An increase in the percentage of chromosome aberrations was found in human lymphocytes treated in vitro with 2,4-D (Korte and Jalal 1982). Although these clastogenic effects were found at concentrations as low as $0.2 \mu\text{g}.\text{mL}^{-1}$ they were statistically significant only at concentrations of $50 \mu\text{g}.\text{mL}^{-1}$ or higher. It is not known how these in vitro doses relate to in vivo exposure.

Based on present knowledge, it is our opinion that dioxin contaminants in 2,4-D are unlikely to be responsible for the development of the reproductive effects observed in laboratory animals exposed to high doses of 2,4-D. The question then arises whether 2,4-D itself is responsible for these effects. Whatever the case, the presence of these effects clearly indicate that precautions should be taken with the use of 2,4-D formulations, even when the dioxin content is low, until the question is resolved. Particularly, women of child-bearing age, as a critical exposure group, need evaluation in any assessment.

Table 2-2. Lack of correlation between dioxin content in 2,4-D derivatives and adverse birth effects in rats (data after Khera and McKinley 1972).

2,4-D	Dose (mg.kg-BW ⁻¹ .d ⁻¹)	Potential dioxin contaminants ^α (ng.kg-BW ⁻¹ .d ⁻¹)	No. of dams	Average fetal BW (g)	Average number of dead fetuses per litter	Average percent skeletal malformations per litter
Vehicle control	-	0	7	5.00	0.3	6
Acid	150	<0.5	10	4.12	2.1	48
Butyl ester	150	≈750	4	4.07	2.5	44
Isooctyl ester	150	≈650	5	3.82	0.8	57

^α Based on data in Table 2-1.

3.0 ISSUE: WHAT IS THE EXPLANATION FOR THE NEUROLOGICAL COMPLAINTS SEEN IN WORKERS EXPOSED TO 2,4-D?

Neurotoxic effects have been reported to be related to exposure to 2,4-D (Goldstein et al. 1959; Todd 1962; Desi et al. 1962; Seabury 1963; Berkeley and Magee 1963; Nielsen et al. 1965; Berwick 1970; Wallis et al. 1970; Kontek et al. 1973; Singer et al. 1982). The reported signs and symptoms include ataxia, reflex disorders, slowed nerve conduction velocity, headache, polyneuritis and peripheral neuropathy. These effects are among the most frequent complaints from industrial and agricultural workers having contact with 2,4-D. High doses of 2,4-D (200 mg.kg-BW⁻¹, approximately 50% of the LD₅₀) have been shown to disturb cerebral electrical activity in rats and cats, and histopathological examinations have revealed degenerative changes in the spinal cords of dead animals (Desi et al. 1962). Myotonic effects are also well documented in mice and rats treated with high doses of 2,4-D (150-200 mg.kg-BW⁻¹) (Bucher 1946; McArdle et al. 1980). These observations suggest that the central nervous system may be a target organ for 2,4-D. Although animal distribution studies have consistently indicated that the concentration of 2,4-D or its metabolites in brain tissue^α is extremely low (<5% relative to plasma) if it is detectable at all (Erne 1966a; Khanna and Fang 1966), neural tissue may be particularly sensitive to 2,4-D.

3.1 NEUROTOXICITY AND TISSUE DISTRIBUTION

The low level of 2,4-D in the brain is partly attributable to the low lipophilicity ($K_{ow}^B = 37$) (Chiou et al. 1977) and ease of ionization, which prevents significant partitioning across the blood-brain barrier. Since 2,4-D is a relatively strong acid with a pK_a of 2.94 (Nelson and Faust 1969), one would expect from the Henderson-Hasselbach equation that at a plasma pH of 7.4, the 2,4-D is largely ionized (>99%). Furthermore, 2,4-D (free acid) has been shown to bind to serum albumin (Erne 1966b; Haque et al. 1975; Mason 1975). Thus, the high degree of ionization and sequestration by protein binding decreases the availability of 2,4-D for diffusion across lipid biomembranes.

To explain the discrepancy between the low concentration in brain tissue and the apparent neurotoxicity, the following hypotheses could be advanced:

^α Paper chromatography was used to determine the nature of the radioactivity in the brain extracts. Aliquots of these were chromatographed in two solvent systems. In both cases, only one radioactive spot which coincided with 2,4-D was observed.

^B Octanol-water coefficient.

- (i) the brain may be particularly sensitive to 2,4-D or its metabolites, resulting in toxicity even at extremely low doses. There is some evidence that ganglion cells are very sensitive to 2,4-D (Nielsen et al. 1965);
- (ii) 2,4-D may influence certain biochemical processes outside the brain, e.g. glucose uptake and utilization, which are linked to normal nervous functions. This hypothesis has not been investigated;
- (iii) 2,4-D may be metabolized to a more lipophilic product such as 2,4-dichlorophenol, which may readily enter the brain. This hypothesis is not supported by the experimental evidence that 2,4-D does not seem to be readily metabolized in many mammalian species, including man (Kohli et al. 1974; Sauerhoff et al. 1977), sheep (Clark et al. 1964), cattle (Lisk et al. 1963) and rat (Khanna and Fang 1966). Zielinski and Fishbein (1967) could not detect the presence of 2,4-dichlorophenol in mice treated with 100 mg 2,4-D.kg-BW⁻¹. Erne (1966b) and more recently, Grunow and Boehme (1974), found a very small fraction of glycine and taurine conjugates in urine samples of rat and pig treated with 2,4-D, but none were present in the plasma samples. Conjugation metabolites are usually less lipophilic and therefore are not expected to cross the blood-brain barrier as readily; they are also readily excreted by the liver or kidney. At very high doses, there could be effects of conjugates on the brain (or other organ systems) because of liver toxicity or renal failure where the conjugates are not properly excreted. This has not been investigated; and
- (iv) there is an increased influx of 2,4-D or related toxicant into the brain following acute exposure at high doses. No information is available on the tissue distribution of 2,4-D, when given to animals at high doses, because most studies were performed with low nontoxic doses, frequently involving a radiolabel. There is some evidence from human forensic data on suicide cases that 2,4-D can occur at relatively high concentrations in the brain; 160% relative to blood was reported by Dudley and Thapar (1972) and 710% relative to blood by Geldmacher et al. (1966). However, there are other cases where the level in the brain was reported to be relatively lower than in the blood (2-13%) (Nielsen et al. 1965; Geldmacher et al. 1966). Since the initial doses of 2,4-D are not known, it is difficult to make comparisons. Redistribution of 2,4-D to the brain may be due to changes in membrane permeability of the blood-brain barrier or to saturation of binding to serum albumin, thereby increasing the concentration gradient of the unbound 2,4-D.

In support of the fourth hypothesis, Elo and Ylitalo (1977, 1979) demonstrated that there was a substantial increase in radioactivity (assumed but not confirmed to be the unchanged parent

compound) in the brains of rats pretreated with high doses of the phenoxy herbicides, ^{14}C -2,4-D and ^{14}C -MCPA $^{\alpha}$ (Table 3-1). The severity of detectable toxic signs increased concomitantly with an increase in radioactivity in the brain and cerebrospinal fluid (CSF). They also found that ^{14}C -MCPA binding to protein in vitro decreased from 77% to 36% following pretreatment with 2-4 mg MCPA.mL^{-1} (approximately equivalent to the plasma concentration following a dose of 500 mg.kg-BW^{-1}). The tissue distribution patterns and mechanisms of MCPA and 2,4-D appear to be very similar and hence parallelism in effects is assumed. Elo and Ylitalo (1979) concluded that the increase in unbound ^{14}C -MCPA probably contributed to the elevation in cerebral ^{14}C concentration and neurotoxicity. Chronic low-level pretreatment similar to that in occupational environments produced no changes in the distribution pattern.

Thus, it appears that the distribution pattern of ^{14}C activity is dose-dependent and is mediated by the extent of protein binding. The binding of 2,4-D to the protein, bovine serum albumin, has been studied by Kolberg et al. (1973), Haque et al. (1975), and Mason (1975). Mason (1975) also showed some similarities between bovine serum albumin and human albumin. Two classes of albumin binding sites for 2,4-D are reported to exist: the high affinity class has a dissociation constant (K_1) of 25×10^{-6} M and 3 binding sites (n_1) and the low affinity class has a K_2 of 1×10^{-2} M and 40 binding sites (n_2). If one assumes that each binding site within the same class has the same affinity and that there is no cooperative effort, then simple mass-action law prevails:

Let $[C]$ = concentration of unbound 2,4-D in plasma
 $[A]$ = concentration of serum albumin
 $[A_1]$ = concentration of high affinity albumin binding sites that are not bound to 2,4-D
 $[A_2]$ = concentration of low affinity albumin binding sites that are not bound to 2,4-D
 $[A_1C]$ = concentration of high affinity albumin binding sites that are bound to 2,4-D
 $[A_2C]$ = concentration of low affinity albumin binding sites that are bound to 2,4-D

All concentrations are in millimolar (mM) and it is assumed that all the sites on the albumin are available for binding to 2,4-D.

$$\begin{aligned} n_1 [A] &= [A_1] + [A_1C] \\ n_2 [A] &= [A_2] + [A_2C] \end{aligned}$$

$^{\alpha}$ MCPA: 2-methyl-4-chlorophenoxyacetic acid.

Table 3-1. Percentage tissue/plasma ratios of ^{14}C -activity in rats pretreated with 2,4-D and MCPA (from Elo and Ylitalo 1979).

Pretreatment ^α	Percentage Tissue/Plasma Ratio		
	Plasma ^β	Brain	Cerebrospinal Fluid
Saline	100	2.3 ± 0.2	0.4 ± 0.1
250 mg 2,4-D.kg-BW ⁻¹	67.4	15.0 ± 1.8	9.4 ± 0.7
Saline	100	1.5 ± 0.1	0.3 ± 0.1
25 mg MCPA.kg-BW ⁻¹	94.7	2.0 ± 0.1	0.9 ± 0.3
100 mg MCPA.kg-BW ⁻¹	70.5	3.9 ± 0.2	2.7 ± 0.3
250 mg MCPA.kg-BW ⁻¹	57.3	16.7 ± 1.1	11.7 ± 0.7
500 mg MCPA.kg-BW ⁻¹	44.9	26.5 ± 0.3	20.2 ± 0.7

^α MCPA or 2,4-D pretreatment dose was administered subcutaneously to adult male rats, and 0.296 MBq (8 mg) of ^{14}C -MCPA.kg-BW⁻¹ or 0.296 MBq (8.8 mg) of ^{14}C -2,4-D.kg-BW⁻¹ was injected intravenously 30 min before the start of CSF collection. CSF was collected for 1 h between 3.5-4.5 h after pretreatment. Radioactivity is expressed in Becquerel (Bq) units (37 GBq = 1 Ci).

^β Plasma ^{14}C -activity is expressed as percentage of that in the plasma of saline-treated controls (=100%).

$$\begin{aligned} \text{since } K_1 &= \frac{[A_1][C]}{[A_1C]} & K_2 &= \frac{[A_2][C]}{[A_2C]} \\ \therefore \frac{n_1[A]}{[A_1C]} &= \frac{K_1}{[C]} + 1 & \text{and} & \frac{n_2[A]}{[A_2C]} = \frac{K_2}{[C]} + 1 \\ \text{or } \frac{[A_1C]}{[A]} &= \frac{n_1}{\frac{K_1}{[C]} + 1} & \text{and} & \frac{[A_2C]}{[A]} = \frac{n_2}{\frac{K_2}{[C]} + 1} \end{aligned}$$

$$\therefore [A_1C] + [A_2C] = [\text{bound 2,4-D}] = \frac{n_1[C][A]}{(K_1 + [C])} + \frac{n_2[C][A]}{(K_2 + [C])}$$

With this equation and given the average serum albumin concentration in man (0.5 mM according to Martin 1965), one can predict the concentration of free unbound 2,4-D as a function of dose (Table 3-2).

The effect of dose on serum albumin binding is shown graphically in Figure 3-1. It is apparent from the graph that doses of 2,4-D below approximately 75 mg.kg-BW⁻¹ produce little change in the fraction of 2,4-D not bound to albumin. However, as the dose is increased above 75 mg.kg-BW⁻¹, binding sites become saturated and the higher the dose of 2,4-D, the greater the fraction that is unbound. It is evident that doses of 2,4-D greater than 75 mg.kg-BW⁻¹ would sharply increase the concentration of unbound 2,4-D, which may then cross the blood-brain barrier to cause injury to the vulnerable ganglion cells. The threshold value of 75 mg.kg-BW⁻¹ may be slightly underestimated because only a fraction of the unbound 2,4-D may diffuse across the blood-brain barrier depending on its degree of ionization. Furthermore, there are other competing processes such as excretion which may lower the total body burden of 2,4-D.

The hypothesis on albumin binding presented here is consistent with the findings of Elo and Ylitalo (1977, 1979), who observed a considerable increase in the radiolabel concentration in the brain after dosing with ¹⁴C-2,4-D and ¹⁴C-MCPA (0.296 MBq of each), and a corresponding increase in neurotoxicity following pretreatment with 250 mg.kg-BW⁻¹ of 2,4-D and 250 and 500 mg.kg-BW⁻¹ of MCPA. These changes were not seen after pretreatment with 25 mg.kg-BW⁻¹ of MCPA or in chronic low level pretreatment. The effects noted by Seabury (1963) also support this hypothesis. When a patient suffering from terminal coccidioidomycosis was treated with progressively larger doses of 2,4-D, he fell into a semi-stuporous state showing neurological and muscular effects. The patient had been treated with a total of 12.7 g (≈152 mg.kg-BW⁻¹) of 2,4-D without any apparent effects before the last 3.6 g (≈51 mg.kg-BW⁻¹) dose caused the lapse. While the hypothesis is not consistent with the neurological complaints of workers who are exposed to low levels of 2,4-D, it is consistent with such effects at high

Table 3-2. The effect of dose on the binding of 2,4-D to albumin.

$[C]^{\alpha}$ (mM)	Total plasma 2,4-D (mmol) (bound and unbound)	Fraction of 2,4-D unbound	Dose $^{\beta}$ (mg.kg-BW $^{-1}$)
0.001	0.061	0.02	4
0.005	0.264	0.02	17
0.01	0.46	0.02	29
0.03	0.91	0.03	58
0.05	1.15	0.04	73
0.10	1.50	0.07	96
0.25	2.10	0.12	134
0.50	2.88	0.17	184
0.75	3.60	0.21	230
1.00	4.28	0.23	273
1.25	4.94	0.25	315
1.50	5.58	0.27	356
2.00	6.81	0.29	434
3.00	9.10	0.33	580
4.00	11.20	0.36	714
5.00	13.16	0.38	839

$^{\alpha}$ $[C]$ = concentration of unbound 2,4-D in plasma (arbitrarily chosen for these calculations).

$^{\beta}$ Dose is estimated by assuming a volume of distribution $V_d = 288.5$ mL.kg $^{-1}$ (Sauerhoff et al. 1977).

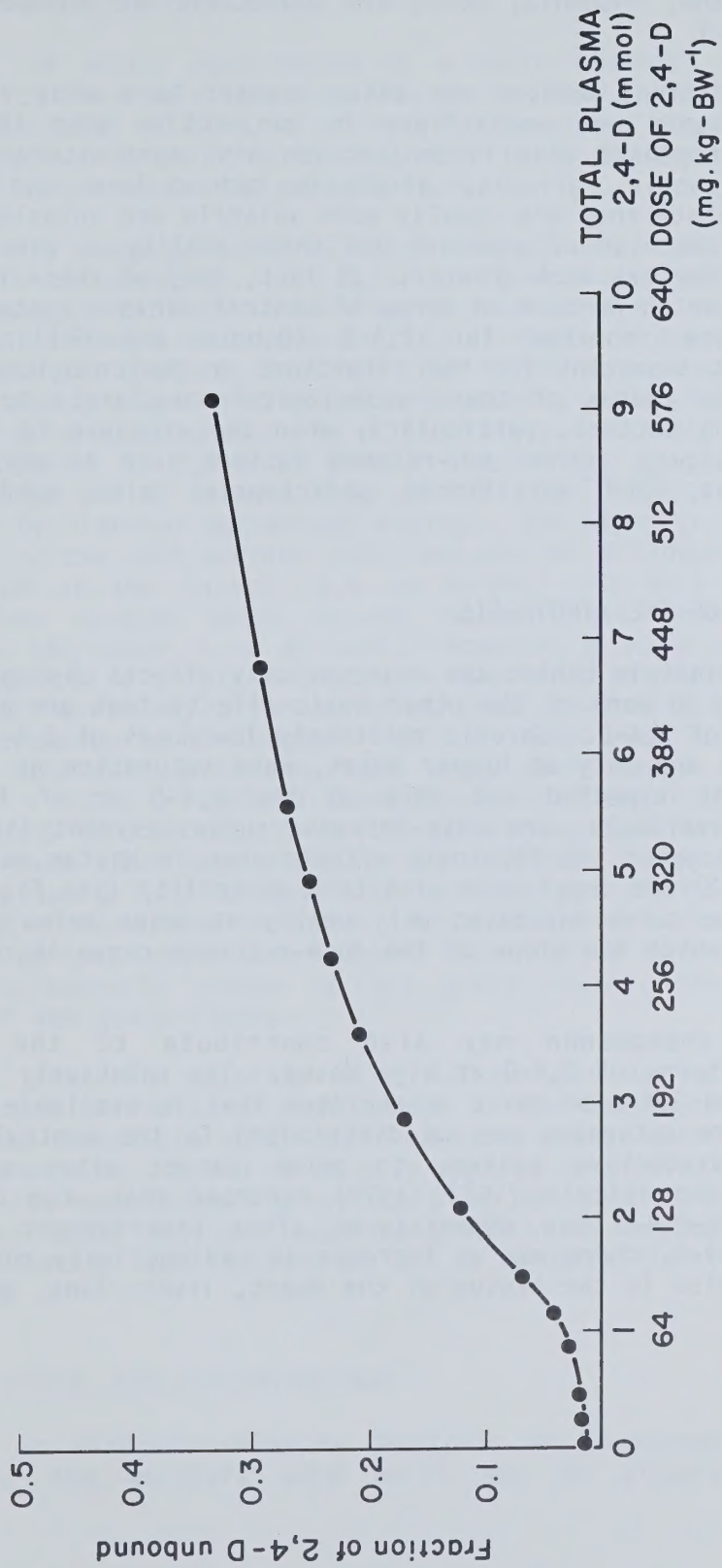


Figure 3-1. The effect of dose on the binding of 2,4-D to albumin.

dosages. It must be emphasized that many of the neurological symptoms, including headache, insomnia, etc., are subjective and nonspecific for exposure to 2,4-D.

In addition, workers are often exposed to a wide variety of pesticides, solvents and emulsifiers in conjunction with the use of 2,4-D. These compounds used in conjunction with agricultural products may include alcohols, glycols, aliphatic hydrocarbons and aromatic hydrocarbons. Since they are usually more volatile and soluble in lipid than is 2,4-D, the risk of exposure and their ability to penetrate the blood-brain barrier are much greater. In fact, many of these industrial solvents are known to produce an array of central nervous system effects similar to those reported for 2,4-D (Dubois and Geiling 1959). Therefore, it is important for the clinicians or toxicologists who are investigating the causes of these neurological complaints to consider these confounding factors, particularly when the exposure to 2,4-D has been at low dosages. Other job-related factors such as physical and thermal stresses, and nutritional deficiencies also need careful evaluation.

3.2 GENERALITY OF THE HYPOTHESIS

The principle behind the neurotoxicity effects discussed above might also apply to many of the other toxic effects that are associated with high doses of 2,4-D. Chronic relatively low doses of 2,4-D produce very few effects and only at higher doses, when saturation of the serum binding sites is expected and more of the 2,4-D or of the toxic metabolites is available, are dose-response curves evident (see Figure 3-1). The teratogenic and fetotoxic effects seen in Wistar rats (Khera and McKinley 1972) are consistent with this generality (see Figure 2-1). The dose-response curve increases only weakly at doses below 50 mg.kg-BW⁻¹.d⁻¹, after which the slope of the dose-response curve is relatively steep.

This phenomenon may also contribute to the general distribution patterns of 2,4-D at high doses. The relatively increased amount of unbound 2,4-D or toxic metabolites that is available when the binding sites are saturated may be distributed to the central nervous system, the reproductive system, to other target sites and/or be excreted. Elo and Ylitalo (1977, 1979) reported that when 0.0296 Bq (8.8 mg) of ¹⁴C-2,4-D was administered after pretreatment with 250 mg.kg-BW⁻¹ of 2,4-D, there was an increase in radioactivity not only in the brain, but also in the tissue of the heart, liver, lung, muscle and testis.

4.0 ISSUE: WHAT IS THE EXPOSURE TO BYSTANDERS FROM THE AERIAL APPLICATION OF 2,4-D?

The aerial application of a toxic chemical inevitably poses some risk to the health of organisms in the area. As described in NRCC (1982), the level of risk is defined by the actual exposure encountered by the organism as well as by its sensitivity to the chemical. It is therefore important to estimate exposure.

The usage patterns of 2,4-D indicate the major exposure groups that may be of concern. Since 2,4-D is extensively used in public parks and on lawns to protect against weeds such as dandelions, the children that frequent these areas are a critical exposure group. Because they usually wear few clothes, roll and play in the grass and may even ingest the dirt and grass, children may encounter a much higher than average exposure in sprayed areas. In a laboratory and field study examining the persistence of 2,4-D on grass, Thompson *et al.* (1983) have shown that only 10 and 5% respectively of the total chemical applied can be dislodged by vigorous mechanical wiping. The majority of 2,4-D applied was found in the leaf surface (72%) and was not dislodged by wiping. An examination of the thatch (1.5 cm height) and soil remaining after cutting the sprayed grass showed insignificant amounts of chemical (< 1%) in the upper 5 cm of soil. However, a study by Taskar *et al.* (1982) reported a 2-fold increase in the soil residues from the first day to the fourth day after spraying with 2,4-D in a field experiment. A rapid decrease in dislodgable residues over time was reported which was much more evident in the field study where levels on grass reached < 1% and < 0.02% of applied chemical within 3 and 7 days respectively. There was 7% left at day 15 in the laboratory experiment. The authors indicate that this was probably due to less photodegradation and/or volatilization or lack of wash with rain or dew. While the authors have shown that children are likely at little risk when walking or sitting on recently sprayed grass they might encounter a higher exposure when playing strenuously enough to get grass stains, hence breaking the surface of the grass blades.

Since the majority of 2,4-D is used in agriculture on the Prairies and on forestry plantations in New Brunswick, the people in these areas constitute other major exposure groups needing consideration in any assessment. 2,4-D is usually applied by aircraft or groundrig on the Prairies and either by aircraft or helicopter in New Brunswick. A computer model has been used to predict the exposure to bystanders from the aerial application of 2,4-D in both the Prairies and New Brunswick.

4.1 THE AERIAL APPLICATION METHOD

An aircraft releases chemicals as an aerosol. A cloud is formed by the aircraft wake which may be dispersed somewhat by

atmospheric turbulence as it descends (Bilanin et al. 1978; Wickens 1980). The spray deposition pattern, and consequently the exposure encountered by various organisms, will thus be affected by atmospheric flow patterns, temperature, spray droplet size and the topography of the area. Even if one ignores the possibility of human errors, which can lead to oversprays, it is obviously difficult to estimate the amount of spray reaching potential receptor organisms.

In the NRCC monograph on aminocarb (NRCC 1982), various scenarios were described from which theoretical "worst-case" exposure to human bystanders can be predicted for the inhalation, dermal and ingestion routes. Because some of the grossest assumptions used in these scenarios were associated with the prediction of the airborne concentrations of the chemical, a computer model was used to refine our predictive capabilities of airborne aminocarb concentrations.

In order to assess bystander exposure from aerial spray applications of 2,4-D, this model has been modified to predict the atmospheric concentration of 2,4-D spray droplets to 800 m from the application site. The model is described in more detail in Appendix I.

4.1.1 AGRICULTURAL SPRAYS vs FOREST SPRAYS

The factors influencing bystander exposure to droplet drift differ between aerial forest insecticide sprays and aerial agricultural herbicide sprays. The application strength of agricultural herbicides is generally higher, and thus higher exposures might be anticipated. However, the droplet diameters are larger in agricultural sprays. Moreover, the spray aircraft is much closer to the vegetation so that the average aircraft wake descent velocity between the aircraft and the ground is higher. These differences might be expected to reduce droplet drift and the resultant exposure to bystanders were it not for the fact that larger droplets are intercepted more efficiently by a bystander's head and arms. In the present computations, these effects are modelled as realistically as possible.

4.2 THE COMPUTER MODEL

4.2.1 MODEL STRUCTURE

The present deposition model is structured differently from the forest spray drift model that was used for aminocarb (NRCC 1982) because the swath width of about 400 m used in aerial forestry sprays is much larger than that used in agricultural spraying. The structure of the model and the reasons for the changes are detailed in Appendix I.

4.2.2 THE SPRAY SCENARIOS

Two scenarios simulating 2,4-D use in Canada are modelled.

- 1) Agricultural application on the Canadian prairies is represented by an aerial spray, using D6-46 nozzles, of 2,4-D (amine) herbicide in aqueous formulation. A spray height of ≈ 1.5 m and a low vegetation height (20 cm) are assumed. The application strength is modelled as $1.96 \text{ kg-AI}^\alpha \cdot \text{ha}^{-1}$ and the formulation strength as $70 \text{ g-AI} \cdot \text{L}^{-1}$ (these are realistic figures; calculated from Franklin et al. 1982). The wind speed (2 m above the ground) and relative humidity are modelled respectively at $1.5 \text{ m} \cdot \text{s}^{-1}$ and 80%, representing an early morning situation, and at $3.0 \text{ m} \cdot \text{s}^{-1}$ and 40%, representing a situation at midday (from Franklin et al. 1982).
- 2) Application in New Brunswick is simulated as an aerial spray, using Teejet nozzles, of a 2,4-D/2,4,5-T mixture (50:50) (both esters) in aqueous formulation on a tree plantation for conifer release ^{β} . A spray height of $\approx 6-9$ m and a large vegetation height (1.5 m) are assumed. The application strength is modelled as $1.68 \text{ kg-AI} \cdot \text{ha}^{-1}$ and the formulation strength as $45 \text{ g-AI} \cdot \text{L}^{-1}$ (these are realistic figures; McDonald 1982). The wind speed (2 m above the ground) and relative humidity are modelled as $1.5 \text{ m} \cdot \text{s}^{-1}$ and 80% (Bowser 1982) respectively, appropriate to an early morning spray. Little aerial application of herbicide is conducted in New Brunswick in windier conditions (Environment New Brunswick 1983) because of the proximity of nontarget receptors.

The initial distribution of droplet numbers and sizes in the drift cloud depends on the atomizing nozzles used to generate them. Here, droplet size and number distributions from two nozzles are considered. The droplet size distributions from the D6-46 nozzle and the Teejet nozzle, assumed to be representative of the Prairie and New Brunswick cases respectively, are given in Appendix I.

4.3 MODEL-PREDICTED BYSTANDER EXPOSURE

For each of the scenarios, the exposure to bystanders was calculated at 50, 100, 200, 400, and 800 m downwind. The calculations for exposure assumed a target volume enclosing the head, neck and arms. This extended from 1.0 to 1.8 m vertically, and was 0.8 m deep and 0.8 m wide. The model computes the number of airborne droplets of each size class in the target volumes as a function of time after spray. As in the forest spray exposure computations for aminocarb (NRCC 1982), the

^{α} AI = active ingredient.

^{β} Conifer release means the killing of broad-leaved hardwood seedlings to allow the conifers to grow without competition.

bystander's head and neck were modelled as a flat plate 50 cm high and 20 cm wide, and the two arms as a vertical plate 200 cm long and 9 cm wide. The collection efficiency of these surfaces to windblown droplets was modelled, as before, after Langmuir (1945) to determine the dermal exposure. The time-integrated concentration of droplets in the target (specified) volumes was also calculated to determine oral and inhalation exposure.

4.3.1 MODEL RESULTS

The dermal, oral and inhalation exposures predicted for a single spray swath are tabulated for the Prairie scenario (Table 4-1) and for the New Brunswick (N.B.) scenario (Table 4-2).

As detailed in NRCC (1982), inhalation exposure may result from the respirable droplet component of the spray cloud and/or from vaporization of the chemical during and after deposition (Houghton 1978). The exact dimensions of the particles are open to debate and for the present calculations (Tables 4-1 to 4-3), inhalation exposure is assumed to occur from droplets initially in the 0-25 μm size class (0-11.25 μm evaporated diameter) and oral exposure from droplets initially between 25 and 116.67 μm (11.25 to 52.50 μm evaporated diameter). Oral exposure occurs from the larger droplets that are lodged higher in the respiratory system and are subsequently swallowed. Particles larger than 116.67 μm fall too rapidly to be inhaled.

4.3.2 EXPOSURE CALCULATIONS

In order to estimate exposure in units that can be related to toxicology data for estimating risk, a "standard" bystander must be conjectured. In the aminocarb monograph (NRCC 1982), the calculation assumed a 70-kg man with an exposed surface area as detailed earlier and with a respiration rate of 29 $\text{L}\cdot\text{min}^{-1}$ (Franklin et al. 1981).

Estimated exposure for the "standard" man for each of the scenarios and exposure routes has been calculated (Tables 4-3 and 4-4).

4.4 DISCUSSION OF MODEL RESULTS

The predictions (Table 4-1, 4-2 and 4-3) generally reveal much higher exposure to bystanders from dermal impaction of droplets than from oral ingestion or inhalation for both the N.B. and Prairie scenarios. At the current application rates of aminocarb ($70 \text{ g}\cdot\text{AI}\cdot\text{ha}^{-1}$) total bystander exposure to aminocarb forest spray from Teejet nozzles on spray aircraft flying "out of ground effect" ^{α} was predicted to be

^{α}

An aircraft flying "out of ground effect" is flying high enough to allow roll-up of the vortex sheet into the vortex wake with reduced descent velocity.

Table 4-1. Exposure to bystanders from an aerial spray of 2,4-D, as predicted by the model using the Prairie scenario.

Distance from spray line (m)	Wind speed at 2 m agl ^α (m.s ⁻¹)	Exposure		
		Dermal (μg)	Oral ^β (μg.min.L ⁻¹)	Inhalation ^β (μg.min.L ⁻¹)
50	1.5	1.36	2.68×10^{-3}	1.35×10^{-5}
	3.0	100.60	1.93×10^{-3}	9.57×10^{-6}
100	1.5	0.32	1.37×10^{-3}	8.53×10^{-6}
	3.0	19.08	1.08×10^{-3}	5.03×10^{-6}
200	1.5	0.058	4.37×10^{-4}	4.32×10^{-6}
	3.0	3.06	4.70×10^{-4}	2.77×10^{-6}
400	1.5	0.010	1.52×10^{-4}	1.87×10^{-6}
	3.0	0.55	1.38×10^{-4}	1.20×10^{-6}
800	1.5	0.002	5.06×10^{-5}	8.57×10^{-7}
	3.0	0.18	4.78×10^{-5}	3.57×10^{-7}

^α agl = above ground level.

^β The units are time-integrated atmospheric concentrations of herbicide; the mass of pesticide ingested is determined by multiplying by the breathing rate.

Table 4-2. Exposure to bystanders from an aerial spray of 2,4-D, as predicted by the model using the New Brunswick scenario.

Distance from Spray line (m)	Windspeed at 2 m agl (m.s ⁻¹)	Exposure		
		Dermal (μg)	Oral ($\mu\text{g}.\text{min}.\text{L}^{-1}$)	Inhalation ($\mu\text{g}.\text{min}.\text{L}^{-1}$)
50	1.5	42.52	0.483	0.069
100	1.5	5.27	0.218	0.037
200	1.5	2.11	0.098	0.013
400	1.5	0.64	0.023	0.005
800	1.5	0.02	0.011	0.002

Table 4-3. Estimated "worst-case" exposure^α (dermal, oral and inhalation) to bystanders.

Distance from spray Line (m)	Windspeed at 2 m agl (m.s ⁻¹)	Dermal Exposure		Oral Exposure ^β		Inhalation Exposure ^β	
		Prairie Scenario	N.B. Scenario	Prairie Scenario	N.B. Scenario	Prairie Scenario	N.B. Scenario
50	1.5	1.94 x 10 ⁻⁵	6.07 x 10 ⁻⁴	1.11 x 10 ⁻⁶	2.00 x 10 ⁻⁴	5.59 x 10 ⁻⁹	2.86 x 10 ⁻⁵
	3.0	1.44 x 10 ⁻³		7.99 x 10 ⁻⁷		3.96 x 10 ⁻⁹	
100	1.5	4.57 x 10 ⁻⁶	7.53 x 10 ⁻⁵	5.67 x 10 ⁻⁷	9.03 x 10 ⁻⁵	3.53 x 10 ⁻⁹	1.53 x 10 ⁻⁵
	3.0	2.73 x 10 ⁻⁴		4.47 x 10 ⁻⁷		2.08 x 10 ⁻⁹	
200	1.5	8.29 x 10 ⁻⁷	3.01 x 10 ⁻⁵	1.81 x 10 ⁻⁷	4.06 x 10 ⁻⁵	1.79 x 10 ⁻⁹	5.38 x 10 ⁻⁶
	3.0	4.37 x 10 ⁻⁵		1.95 x 10 ⁻⁷		1.15 x 10 ⁻⁹	
400	1.5	1.43 x 10 ⁻⁷	9.14 x 10 ⁻⁶	6.29 x 10 ⁻⁸	9.52 x 10 ⁻⁶	7.74 x 10 ⁻¹⁰	2.07 x 10 ⁻⁶
	3.0	7.86 x 10 ⁻⁶		5.71 x 10 ⁻⁸		4.97 x 10 ⁻¹⁰	
800	1.5	2.86 x 10 ⁻⁸	2.86 x 10 ⁻⁷	2.09 x 10 ⁻⁸	4.55 x 10 ⁻⁶	3.55 x 10 ⁻¹⁰	8.28 x 10 ⁻⁷
	3.0	2.57 x 10 ⁻⁶		1.98 x 10 ⁻⁸		1.48 x 10 ⁻¹⁰	

^α The exposures are calculated for the time taken for the spray drift cloud to cross the target. The time period extends from a 0.25 to 1.5 minutes depending on the droplet size, the windspeed and the distance from the spray line.

^β At a respiration rate of 29 L.min⁻¹.

Table 4-4. Estimated "worst-case" total exposure to bystanders from one swath.

Distance from Spray Line (m)	Windspeed at 2 m agl (m.s ⁻¹)	Total Exposure (mg.kg-BW ⁻¹)	
		Prairie Scenario	N.B. Scenario
50	1.5	2.05×10^{-5}	8.36×10^{-4}
	3.0	1.44×10^{-3}	
100	1.5	5.14×10^{-6}	1.81×10^{-4}
	3.0	2.73×10^{-4}	
200	1.5	1.01×10^{-6}	7.61×10^{-5}
	3.0	4.39×10^{-5}	
400	1.5	2.07×10^{-7}	2.07×10^{-5}
	3.0	7.92×10^{-6}	
800	1.5	4.99×10^{-8}	5.66×10^{-6}
	3.0	2.59×10^{-6}	

19.6 μg at 400 m at a wind speed of 1 m.s^{-1} (NRCC 1982). This can be compared with an exposure of 0.67 μg at a wind speed of 1.5 m.s^{-1} in the presently considered 2,4-D N.B. scenario (application rate of 1680 g-AI.ha^{-1}) with the spray aircraft flying "in ground effect". The difference is largely due to the higher average downwash velocity of the low-flying aircraft applying herbicide which serves to reduce wind drift. Another significant reason is the difference in the droplet size distributions. Although the distributions from both the aminocarb forest spray and the herbicide spray are generated by a Teejet nozzle, the present computations take account of the much higher than suspected fraction of the spray mass in droplets under 50 μm diameter revealed by the recent laser spectrometer data of Picot (1983). Small droplets have very low impaction efficiency, thus lowering the dermal and hence overall exposure relative to the earlier forest pesticide spray model computations.

Overall, the present model predicts higher exposure from the N.B. Teejet spray than from the Prairie D6-46 spray. This result is almost entirely due to the different droplet size distributions from the two nozzles; the Teejet spectrum has 85% of the spray volume in droplets under 217 ^{α} μm diameter, the D6-46 only 3.7%.

4.4.1 EXPOSURE RISK DUE TO DRIFT

The computer model was used to predict exposure to bystanders at 50, 100, 200, 400 and 800 m from the spray line. In the Prairie case, where estimations are made at wind speeds of 1.5 and 3.0 m.s^{-1} , the total exposure at distances up to 200 m is 2 orders of magnitude higher at 3.0 m.s^{-1} . By 800 m from the spray line, the exposure had decreased greatly, from 100-10 000-fold, depending on the wind speed and the scenario. At the given application rates, the computer-estimated total exposure to bystanders at 800 m from the spray line and a wind speed of 1.5 m.s^{-1} is $4.99 \times 10^{-8} \text{ mg.kg-BW}^{-1}$ and $5.66 \times 10^{-6} \text{ mg.kg-BW}^{-1}$ in the Prairie and N.B. scenarios, respectively.

The question of drift from aerial spraying of pesticides has been an issue for a long time. In New Brunswick, spraying of 2,4-D or a 2,4-D/2,4,5-T mixture by fixed-wing aircraft must be conducted on spray blocks at a minimum distance of 2.7 miles (1.6 km) and 5 miles (8 km), respectively, from any human habitation (Environment New Brunswick 1983). Using the computer estimations and the wind speeds used in these scenarios, the bystander exposure at two and a half or five miles from the spray line would be almost negligible (i.e. $6 \times 10^{-6} \text{ mg.kg-BW}^{-1}$ at 800 m).

^{α} Droplets larger than $\approx 200 \mu\text{m}$ in diameter are assumed, in these computations, to fall too rapidly to be entrained into the vortex wake and cause bystander exposure. The upper limit is 217 μm for the size range centered on 200 μm .

4.4.2 EFFECT OF MULTIPLE SWATHS

The spray swath nearest to a bystander contributes most to the exposure. However, the tabulated results may be used to predict bystander exposure to a multiple swath operation. An example is shown below (Table 4-5) for a total of 10 swaths spaced at 15 m intervals in the Prairie scenario with a 2-m^α wind speed of 3.0 m.s⁻¹. Only the dermal impaction is considered since this is the chief component of bystander exposure. However, other exposure components will vary in approximately the same manner. The effect on the dermal exposure of additional upwind swaths becomes increasingly smaller. For a bystander at 50 m, 10 swaths lead to a dermal exposure of 282.34 µg, compared with 100.60 µg for one swath. At 800 m however, the effect of 10 swaths is approximately ten times the effect of one swath, for a dermal exposure of ≈1.8 µg.

4.4.3 VALIDITY OF RESULTS

It must be recognized that the computer-model exposure estimates apply only for the stated scenarios and only for ideal spraying operations. Historically, such conditions have not always existed. Problems include irregular spray patterns causing deposition in non-target areas (NRCC 1975; EPS 1976); spillage and leakage of the pesticide during mixing and loading (EPS 1976; Stuart 1977); incorrect mixing and hence, incorrect formulations (Stuart 1977); unquantified and unstandardized application techniques (e.g. nozzle types) causing unknown exposure; and pesticide spills resulting from emergency dumping or aircraft crashes (Stuart and Gamble 1977).

4.5 COMPARISON WITH FIELD DATA

Maybank et al. (1978) described a field experiment studying windborne drift from an aerial spray of 2,4-D on the Canadian Prairies. They estimated that 5% of the AI would remain airborne at 200 m in a 2-m wind speed of 3.1 m.s⁻¹. Since the nozzle type and the droplet spectrum were not reported, strict comparisons with the computer model results are not possible. Nevertheless, for their particular scenario, the computer model predicts 0.059% and 42.6% of the AI from the D6-46 and Teejet nozzle spectrums, respectively, to be airborne at 200 m. These results suggest that the droplet-size distribution in the Maybank et al. (1978) study lay between that of the Teejet and the D6-46 nozzles.

Recently, a number of exposure studies on 2,4-D have been published, several of which can be compared on a gross level with the results of the computer model (Table 4-6). The numbers are not directly comparable due to differences in application equipment and study design. As would be expected, the exposure to the flagmen at the sprayline reported by Franklin et al. (1982) (dermal exposure = 3.26×10^{-1}

^α 2 m above ground level.

Table 4-5. Predicted dermal exposure at 50 m from the spray block^α.

No. of Swaths	Dermal Exposure (μg)
1	100.60
2	175.30
3	213.05
4	235.84
5	249.40
6	259.45
7	267.63
8	274.06
9	278.87
10	282.34

^α Wind speed = 3.0 m.s⁻¹ at 2 m above ground level.

Table 4-6. Comparison of model results with field data.

Occupation	Distance from sprayline (m)	Application rate (kg.AI.ha ⁻¹)	Wind Speed (m.s ⁻¹)	Exposure			Reference
				Dermal	Inhalation	Total	
				(mg.kg-BW ⁻¹)			
bystander ^α (fixed-wing) agric.	50	1.96 1.96	1.5 3.0	1.94x10 ⁻⁵ 1.44x10 ⁻³	5.59x10 ⁻⁹ 3.96x10 ⁻⁹	2.05x10 ^{-5β} 1.44x10 ^{-3β}	Computer-model computations
forest		1.68	1.5	6.07x10 ⁻⁴	2.86x10 ⁻⁵	8.36x10 ^{-4β}	
flagman ^{γ,δ} (fixed-wing) forest	0	2.24 2.24 1.68	2.8 1.4 1.4	3.26x10 ⁻¹ - -	8.9x10 ⁻⁴ 1.24x10 ⁻⁴ 1.05x10 ⁻³	3.27x10 ⁻¹ - 7.96x10 ⁻¹	Franklin <u>et al.</u> (1982) "
bystander ^{γ,α} (helicopter) forest	10	1.62	"nil"	1.56x10 ⁻¹	-	-	Frank <u>et al.</u> (1983)
observers ^α (helicopter)	20-150	2.2	"calm"	1.0x10 ⁻⁴ - 1.4x10 ⁻³	nd ^ε	-	Lavy <u>et al.</u> (1982)

^α Head, neck and arms exposed.

^β Also includes oral exposure.

^γ Average of two persons.

^δ Neck, arms, chest and legs exposed.

^ε Limit of detection of 5x10⁻⁵ mg.

mg.kg-BW⁻¹) and Frank et al. (1983) (dermal exposure = 1.56×10^{-1} mg.kg-BW⁻¹) was several orders of magnitude higher than the computer-model predicted exposure to a bystander at 50 m from the sprayline. Lavy et al. (1982) reported the dermal exposure encountered by observers at 20-150 m from the sprayline as 1.0×10^{-4} - 1.4×10^{-3} mg.kg-BW⁻¹, which is very similar to that estimated for a bystander in our model at 50-100 m from the sprayline^α (4.57×10^{-6} - 6.07×10^{-4} mg.kg-BW⁻¹).

4.6 ADSORBED DOSAGE

Obviously, the dosage that is going to effect the health of an organism is the amount absorbed into its body. For inhalation and oral exposure, it is generally assumed that ≈100% is absorbed through the lungs (Lippman et al. 1980) and across the gastrointestinal tract (Franklin et al. 1981), respectively. The absorption of 2,4-D across the skin has been estimated as ranging from 3% (Frank et al. 1983) to 6% (Feldman and Maibach 1974) of the amount of chemical on the skin. Once the 2,4-D is in the body, it can be assumed that 95-100% of it is excreted within a week (Libich et al. 1982; Leng et al. 1982).

The absorbed dosage for the bystander in our model was estimated using calculations after Frank et al. (1983). Although they assumed that there is no absorption through the head region (because of hair covering) and calculated the average percentage of 2,4-D absorbed through the arms and legs as 3.09%, we will assume that there is absorption through the head, as in our model, giving a percentage absorbed through the arms, legs and head as 2.3%. From our estimations of dermal exposure (Table 4-3) we can then calculate the amount of 2,4-D absorbed (Table 4-7).

4.7 EXPOSURE FROM OTHER METHODS OF APPLICATION

A comparison of exposure groups during both ground and aerial applications (Table 4-8) has confirmed the generally accepted concepts that dermal exposure is the most important route of exposure and that mixers/loaders are the most important group. From the data compared here, it appears that ground sprayers (Libich et al. 1982) are exposed

^α The model predictions are sensitive to the schedule of 'weights' (Appendix I) applied to the nozzles to represent the fraction of their emission entrained by the trailing vortices. For example, in the highly unlikely event that 100% of all emissions is entrained and drifts, the predicted dermal exposure at 100 m would change to 9.99×10^{-6} mg.kg-BW⁻¹ from 4.57×10^{-6} mg.kg-BW⁻¹. In reality, differences in initial droplet size distribution and evaporative characteristics will also be important.

Table 4-7. Estimated absorbed dose of 2,4-D.

Distance from the spray line (m)	Wind- speed (m.s ⁻¹)	Prairie Scenario		New Brunswick Scenario	
		Dermal Exposure	Absorbed Dose (mg.kg-BW ⁻¹)	Dermal Exposure	Absorbed Dose
50	1.5	1.94x10 ⁻⁵	4.46x10 ⁻⁷	6.07x10 ⁻⁴	1.4x10 ⁻⁵
	3.0	1.44x10 ⁻³	3.3x10 ⁻⁵		
100	1.5	4.57x10 ⁻⁶	1.05x10 ⁻⁷	7.53x10 ⁻⁵	1.73x10 ⁻⁶
	3.0	2.73x10 ⁻⁴	6.28x10 ⁻⁶		
200	1.5	8.29x10 ⁻⁷	1.91x10 ⁻⁸	3.01x10 ⁻⁵	6.92x10 ⁻⁷
	3.0	4.37x10 ⁻⁵	1.01x10 ⁻⁶		
400	1.5	1.43x10 ⁻⁷	3.29x10 ⁻⁹	9.14x10 ⁻⁶	2.10x10 ⁻⁷
	3.0	7.86x10 ⁻⁶	1.81x10 ⁻⁷		
800	1.5	2.86x10 ⁻⁸	6.58x10 ⁻¹⁰	2.86x10 ⁻⁷	6.58x10 ⁻⁹
	3.0	2.57x10 ⁻⁶	5.91x10 ⁻⁸		

Table 4-8(a). Comparison of exposure groups^α (aerial application).

Group	Application Rate (2,4-D) (kg-AI.ha ⁻¹)	Potential Exposure Dermal (mg.kg-BW ⁻¹)	Potential Exposure Inhalation (mg.kg-BW ⁻¹)	Amount in Urine (mg.kg ⁻¹ per exposure)	Reference
<u>aerial</u>					
<u>fixed-wing</u>					
<u>(wheat)</u>					
pilot	1.68-2.24	1.9x10 ⁻²	1.09x10 ⁻⁴	9.67x10 ⁻³	Franklin <u>et al.</u> (1982)
pilot	360 kg-AI applied in 14 hrs	-	-	6.0x10 ^{-3B}	Nash <u>et al.</u> (1982)
mixer	1.68-2.24	4.33x10 ⁻¹	3.10x10 ⁻⁴	3.88x10 ⁻²	Franklin <u>et al.</u> (1982)
mixer/loader	585 kg-AI applied in 20 hrs	-	-	1.96x10 ^{-2B}	Nash <u>et al.</u> (1982)
water carrier	1.68-2.24	2.7x10 ⁻²	8.4x10 ⁻⁴	4.25x10 ⁻³	Franklin <u>et al.</u> (1982)
flagmen	"	3.26x10 ⁻¹	6.88x10 ⁻⁴	4.44x10 ⁻³	"
<u>helicopter</u>					
<u>(forest)</u>					
pilot	2.2	5x10 ⁻⁴	nd ^Y	1.98x10 ⁻²	Lavy <u>et al.</u> (1982)
mechanic	"	2.33x10 ⁻²	nd ^Y	5.45x10 ⁻³	"
mixer/loader	"	4.48x10 ⁻²	1.0x10 ⁻¹	1.96x10 ⁻²	"
supervisor	"	2.0x10 ⁻⁴	nd ^Y	2.31x10 ⁻³	"
observer (20-150 m)	"	1.0x10 ⁻⁴	nd ^Y	4.9x10 ⁻⁴	"
pilot 1 ^δ	2,4,5-T	1.1x10 ⁻¹	nd ^ζ	5.0x10 ⁻³	Lavy <u>et al.</u> (1980)
2 ^ε	2.24	nd ^ζ	nd ^ζ	3.8x10 ⁻²	
mixer 1	"	1.2x10 ⁻¹	nd ^ζ	6.5x10 ⁻²	"
2	"	4.2x10 ⁻²	nd ^ζ	9.6x10 ⁻²	"
supervisor 1	"	2.4x10 ⁻²	nd ^ζ	4.0x10 ⁻³	"
2	"	nd ^ζ	nd ^ζ	3.0x10 ⁻³	"
flagmen 1	"	nd ^ζ	nd ^ζ	1.5x10 ⁻³	"
2	"	nd ^ζ	5.15x10 ⁻¹	1.0x10 ⁻³	"

^α Various levels of protective clothing were worn, usually leg, neck, arms exposed.

^Y Limit of detection is 0.05 µg.

^ε Raindrop helicopter.

^B Amount in urine per day not per exposure.

^δ Microfoil helicopter.

^ζ Limit of detection unknown.

Table 4-8(b). Comparison of exposure groups^a (ground application).

Group	Application Rate (kg-AI.ha ⁻¹)	Potential Dermal Exposure (mg.kg-BW)	Exposure Inhalation	Amount in Urine (mg.kg ⁻¹ per exposure)	Reference
tank trucks					
driver	0.5 AI of 2,4-D/gal formulation -mixed with dicamba	4.6x10 ^{-2B}	8.0x10 ⁻⁵	4.0x10 ⁻²	Draper and Street (1982)
mixer/loader/sprayer	"	1.0x10 ^{-1B}	8.8x10 ⁻⁵	1.6x10 ⁻¹	"
mixer/loader/applicator	38 kg-AI applied in 7.9 hr	-	-	1.8x10 ^{-2Y}	Nash <u>et al.</u> (1982)
mixer/loader	18 kg-AI applied in 2.4 hr	-	-	7.0x10 ^{-3Y}	"
applicator	34 kg-AI applied in 3.5 hr	-	-	5.0x10 ^{-3Y}	"
forestry					
mixer/loader	-	-	-	3.8x10 ⁻² - 5.6x10 ⁻²	Lavy <u>et al.</u> (1981)
wheat					
mixer/loader	-	-	-	2.0x10 ⁻²	Anon (1981)
<u>2,4-D/ picloram/ dichlorprop</u>					
truck					
sprayer (gun) roadside	-	2.8x10 ⁻²	6.14x10 ⁻⁴	2.8x10 ^{-2Y}	Libich <u>et al.</u> (1982) ^δ
R.O.W.	-	3.3x10 ⁻²	1.16x10 ⁻³	3.4x10 ^{-2Y}	"
mist-blower R.O.W.	-	4.6x10 ⁻²	4.73x10 ⁻³	5.1x10 ^{-2Y}	"
<u>2,4,5-T</u>					
backpack sprayer	1.79	1.27	1.5x10 ⁻³	4.7x10 ⁻²	Lavy <u>et al.</u> (1980)
supervisor/mixer	"	3.1	nd ^E	1.0x10 ⁻²	"
mist-blower					
supervisor	2.24	2.0x10 ⁻¹	1.1x10 ⁻⁴	2.9x10 ⁻²	"
driver	"	1.29	2.7x10 ⁻⁴	3.5x10 ⁻²	"
mixer	"	1.62	1.9x10 ⁻⁴	7.8x10 ⁻²	"

^a Various levels of protective clothing worn, often no gloves.

^B Dislodgable residues.

^Y Amount in urine per day not per exposure.

^δ Using complete protective equipment.

^E Limit of detection not given.

to 2,4-D at the same order of magnitude as some mixer/loaders. Ground spraying is done mostly along highways, along transmission lines and in public parks.

4.8 AMBIENT EXPOSURE

One would expect the levels of 2,4-D to which the general public is exposed to differ greatly depending upon the geographic area and season. Residues of 2,4-D in surface water are a result of direct and indirect applications of pesticides, agricultural runoff and industrial discharges (Edwards 1973). An examination of surface waters in 12 regions of Western Canada (Gummer 1979) has shown that levels range from 0.004-0.235 $\mu\text{g.L}^{-1}$ with the mean being 0.046 $\mu\text{g.L}^{-1}$. The highest levels were found in Wascana Creek below Regina, Saskatchewan, and in the Red River near Selkirk, Manitoba. Both these rivers had effluent flowing into them from industrial plants: a herbicide packaging plant in the case of Manitoba and a Uniroyal Limited plant in Alberta in the case of Saskatchewan. The NAS (1977) has suggested a no-adverse-effect level of 0.09 mg.L^{-1} for 2,4-D in drinking water. The levels in surface waters in some areas of western Canada are considerably higher than this.

To calculate the average per person consumption of 2,4-D via water we assume that a person consumes 2 litres of surface water a day and weighs 70 kg. This gives a average consumption of 1.14×10^{-4} - 6.71×10^{-3} $\mu\text{g.kg-BW}^{-1}\text{.d}^{-1}$. The effects of the finishing process (filtering and chlorinating) on the levels of 2,4-D in the water are unknown and for our calculations, we have assumed they have no effect.

Atmospheric residue levels in samples taken on the Canadian Prairies or the western U.S. were mostly in the 0.01-1.0 $\mu\text{g.m}^{-3}$ range with some in the 1 $\mu\text{g.m}^{-3}$ level and a very few exceeding 10 $\mu\text{g.m}^{-3}$ (NRCC 1978). The Threshold Limit Value (ACGIH 1980) for 2,4-D has been set at 10 mg.m^{-3} . Assuming the worst-case of a 10 $\mu\text{g.m}^{-3}$ level, the inhalation dose for a 70-kg man would be 4.0×10^{-3} $\text{mg.kg-BW}^{-1}\text{.d}^{-1}$. This is of the same order of magnitude as the backpack sprayer in Lavy *et al.* (1980) (see Table 4-8(b)) although the level of 10 $\mu\text{g.m}^{-3}$ is the worst-case and 0.1-1.0 $\mu\text{g.m}^{-3}$ is more common, giving an inhalation dose of 10-100 fold lower.

5.0 ISSUE: WHAT IS THE STRENGTH OF THE ASSOCIATION BETWEEN PHENOXY HERBICIDES AND DISEASE?

Numerous epidemiological reports have been published suggesting a linkage between phenoxy herbicides and human health effects. In this chapter, we attempt to critically review and analyse them. As there are many difficulties in interpreting epidemiological studies, anyone unfamiliar with epidemiology is referred to Appendix II for a brief overview.

5.1 REVIEW OF POPULATION STUDIES ON 2,4-D

5.1.1 CASE STUDIES

In 1979, Hardell reported that of 17 patients diagnosed with malignant lymphoma in Sweden, 14 had a current occupation which involved the use of phenoxyacids or chlorophenols, e.g. farming, forestry or sawmills. These observations led Hardell to carry out a much larger controlled study in 1981 (discussed in Section 5.1.3).

In 1971, Poland et al. (1971) examined 73 workers at a 2,4-D, 2,4,5-T plant in the United States. As shown in Table 5-1, they found some abnormalities in the workers but, since the study did not use comparison groups, we do not know if the frequency of these findings is unusual. There were also several variables not considered in this study, for example, many of the original workers at the plant had left, and there were differences in the length of employment for the workers studied, e.g. 33 workers were employed at the plant for less than 4 years. Although this makes it difficult to estimate the duration of exposure and limits the analysis to the assessment of short-term effects, comparison groups could have been made up of workers with different lengths of employment. Furthermore, workers were employed at different locations within the plant and unless one could assume similar exposure at the different locations, it would have been preferable to perform a separate analysis with respect to location. This, however, was not possible because of the small numbers of workers.

The health status of 15 workers employed in the packaging of the powered sodium salt of 2,4-D in a plant in Poland were examined (Andreasik et al. 1979). The only quantitative data given for the study was that the workers' age group was between 31 and 58 years, their duration of exposure was between 13 and 29 months and their urinary levels of 2,4-D and the sodium salt of 2,4-D ranged from traces to 40 mg.d⁻¹. This report can be used only as a description of short-term effects because it gives no numerical estimate of risks or effects, and has no control group nor evaluation of confounding factors. The workers were reported as having possible nervous system, respiratory and partial endocrine effects as well as many visceral symptoms. The results of this study initiated a change in the usage of 2,4-D from the powdered formulation to the less toxic fluid form.

Table 5-1. Review of epidemiological studies on 2,4-D.

Reference	Type of study	Description	Number of subjects	Controls	Exposure	Principal Findings																								
Poland et al. 1971	Descriptive	Health survey	73	0	Mixture of 2,4-D, 2,4,5-T and precursors	Severe chloracne in 18%; minimal chloracne 35/73; active chloracne correlated with presence of scarring, hyperpigmentation, hirsutism and complaints of eye irritation Active chloracne not correlated with length of employment; active chloracne not more frequent in those with history of teenage acne 15/73 had history of eye irritation, 3/73 had conjunctival injection, 31.5% had hyperemia of nasal mucosa, 10.9% had inflammation of buccal mucosa 30 had hyperpigmentation, 16 hirsutism Excretion of porphyrins was increased in maintenance men 20/73 had evidence of chronic obstructive pulmonary disease but all were smokers (bronchitis, asthma). 10 subjects had minor liver function abnormalities; 2 were alcohol related 30% of workers complained of gastrointestinal disturbance No major neurological abnormalities were detected 10.3% of workers had abnormal glucose tolerance tests																								
Axelsson et al. 1980	Historical prospective	Update on Swedish Railway workers	348 (5541 person-years)		3 groups: 1. amitrol 2. phenoxyacids (PHA) 3. amitrol and PHA	<u>Total groups</u> Observed deaths = 45 Expected deaths = 49 Observed # tumors = 17 Expected # = 11.85 <u>10-year latency period</u> <table><thead><tr><th></th><th colspan="2">Deaths</th></tr><tr><th>Group</th><th>Obs</th><th>Exp</th></tr></thead><tbody><tr><td>Amitrol group</td><td></td><td></td></tr><tr><td>lung cancer</td><td>1</td><td>0.38</td></tr><tr><td>Phenoxy acid (PHA)</td><td></td><td></td></tr><tr><td>stomach cancer</td><td>2</td><td>0.33</td></tr><tr><td>Amitrol & PHA</td><td></td><td></td></tr><tr><td>all tumors</td><td>6</td><td>1.78</td></tr></tbody></table>		Deaths		Group	Obs	Exp	Amitrol group			lung cancer	1	0.38	Phenoxy acid (PHA)			stomach cancer	2	0.33	Amitrol & PHA			all tumors	6	1.78
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Riihimäki et al. 1982	Historical prospective	Herbicide applicators compared to general population	1971 (16,694 person-years)	General population	2,4-D and 2,4,5-T	<table><thead><tr><th rowspan="2">Cause of death</th><th colspan="2">(10 a)^a</th><th colspan="2">Deaths (15 a)^a</th></tr><tr><th>Obs</th><th>Exp</th><th>Obs</th><th>Exp</th></tr></thead><tbody><tr><td>All causes</td><td>88</td><td>118.6</td><td>35</td><td>53.6</td></tr><tr><td>All cancers</td><td>20</td><td>24.3</td><td>5</td><td>11.3</td></tr><tr><td>Lung cancer</td><td>12</td><td>11.1</td><td>4</td><td>4.7</td></tr></tbody></table>	Cause of death	(10 a) ^a		Deaths (15 a) ^a		Obs	Exp	Obs	Exp	All causes	88	118.6	35	53.6	All cancers	20	24.3	5	11.3	Lung cancer	12	11.1	4	4.7
Cause of death	(10 a) ^a		Deaths (15 a) ^a																											
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Lung cancer	12	11.1	4	4.7																										
Hardell and Sandstrom 1979	Case-control	Patients with soft-tissue sarcoma compared with controls	52	208 matched (age, sex, residence)	PHA and chlorophenols	Risk ratio for soft-tissue sarcoma after exposure to PHA or chlorophenols = 6.2 Risk ratio for PHA alone = 5.3 (2.4 - 11.5) 51% of cases were smokers, 48% of controls were smokers																								

Table 5-1. (CONT'D)

Reference	Type of study	Description	Number of subjects	Controls	Exposure	Principal Findings
Eriksson et al. 1981 ^a	Case-control	Patients with soft-tissue sarcoma compared with controls	110	220	PHA and chlorophenols	Exposure to phenoxyacids or chlorophenols in 23% of cases and 6% of controls Risk ratio for soft-tissue sarcoma after exposure to chemicals was 5.1 (2.5 - 10.4) Phenoxyacids alone: risk ratio = 6.8 (2.6 - 17.3) Non-2,4,5-T phenoxyacids; risk ratio = 4.2 (1.3-14.5)^b
Hardell et al. 1981 ^a	Case-control	Patients with malignant lymphomas compared with controls	169	338	PHA and chlorophenols	Exposure to phenoxyacids or chlorophenols in 36% of cases and 10% of controls Relative risk of malignant lymphoma from exposure to these chemicals was 6.0 (3.7 - 9.7) Exposure to phenoxyacids alone: risk ratio = 4.8 (2.9-8.1) Exposure to phenoxyacids < 90 days risk ratio = 4.3 Exposure to phenoxyacids > 90 days risk ratio 7.0 Exposure to phenoxyacids + organic solvents: risk ratio = 11.2 (3.2 - 39.7) Exposure to phenoxyacids + chlorophenols: risk ratio = 8.4 (4.2 - 16.9)
Hardell et al. 1982 ^a	Case-control	Patients with nasopharyngeal cancer or cancer of the nasal cavity compared with controls	71	541	PHA and chlorophenols	Exposure to phenoxyacids: risk ratio = 2.1 (not significant at P < 0.001) Exposure to chlorophenols: risk ratio = 6.7
Cantor 1982	Case-control	Frequency of farming occupation among NHL ^Y cases compared with frequency among controls	774	1961	Agricultural chemicals; including phenoxy herbicides	Farming more common among cases; risk ratio = 1.2 (0.98-1.51) Risk ratio for reticulum cell sarcomas (RCS) in farmers age < 65 was 2.7 (1.54-4.5) Risk ratio for NHL association increased during the 9 year period from 1.2 to 2.7 Higher risk for RCS in counties where: a) high agricultural activity: risk ratio = 3.2 (1.17-8.5) b) small grain acreage and acres treated with insecticides risk ratio = 6.6 (2.8-15.6) c) wheat average: risk ratio = 4.4 (1.83-10.6)

^a Latency period.

^b Calculated by Coggon and Acheson (1982).

^Y NHL = non-Hodgkins deaths.

5.1.2 COHORT STUDIES

There have not been any prospective cohort studies carried out with respect to 2,4-D. However, two studies (Axelson and Sundell 1974; Axelson et al. 1980) could be considered examples of historical prospective studies. The subjects were Swedish railway workers who had been involved with herbicide spraying for at least 45 days between 1952 and 1972. Total mortality and deaths from cancer were compared between the railway worker group and an age- and sex-matched general Swedish population group. Many experts would argue that the general population does not constitute an appropriate control group and that the study should be considered more as a descriptive mortality study.

Axelson and Sundell (1974) identified workers who had accumulated at least 45 days work with herbicides. The workers were classified into three groups according to exposure: exposure to amitrol and combinations, exposure to phenoxyacids and combinations, and exposure to other herbicides and combinations. Thus, overlapping groups were used. The number of person-years was calculated for each exposure group but since the groups were not mutually exclusive, a person may have been counted in more than one classification. The follow-up period used in the calculation of person-years of observation was the time after accumulating 45 working days with herbicides to the time of death or study cutoff date. Since most of the workers used herbicides only periodically, it might have taken several years for any individual to accumulate 45 working days. The total number of person-years was then multiplied by the age-specific death rate for the general population to determine the expected number of deaths. This method could result in a falsely high number of expected deaths because of the miscalculation of person-years. No increase in tumor incidence or mortality was found in this study although the above-mentioned miscalculations make the results questionable.

Axelson et al. (1980) reexamined the experience of the Swedish railway workers. The same 348 railway workers were followed from 1952 to 1978. The time for follow-up in their report was taken from the beginning of employment, not after 45 days of exposure as in the earlier report. Workers were divided into three distinct groups of workers exposed to: 1) phenoxyacids only, 2) amitrol only, or 3) both phenoxyacids and amitrol. The number of person-years was calculated for each group and the observed numbers of deaths and deaths from cancer were compared with the number expected based on cause- and age-specific death rates and cancer death rates in the general population. There were 45 deaths from all cancers observed in the workers and 49 deaths were expected (Table 5-1). The authors attributed this finding to the "healthy worker effect". However, the observed number of deaths from tumors was greater than expected and was confirmed after reanalyzing for a 10-year latency period. In the amitrol-only group there was a small excess of deaths due to lung cancer (not statistically significant) and in the phenoxyacids-only group there was a small excess of deaths due to

stomach cancer (statistically significant at $P < 0.05$). Findings of this type may be interpreted as indicating a different route of exposure: by ingestion in the case of phenoxyacids, and by inhalation for amitrol. Alternatively, the target organs may be different for different chemical compounds. The authors did not indicate if the possibly confounding effects of smoking were considered in the analysis. This is particularly important in the case of amitrol, as cancer of the lung is well known to be strongly associated with cigarette smoking. In addition it is becoming more and more evident that smoking enhances the pathogenetic effects of chemicals on the respiratory tract.

There was no obvious evidence of synergism between amitrol and phenoxyacids. Although synergy between the two chemicals is conceivable, it is equally possible that both are independently carcinogens, or that some vehicle was common to both chemicals. There is also the possibility that contaminants were responsible for the carcinogenic effects.

A cohort study by Barthel (1976) indicated that occupational exposure to pesticides was associated with an increased risk of lung cancer. A later study (Barthel 1981) reported on 1658 agricultural workers from the German Democratic Republic (GDR) who worked with various chemicals for at least five years between 1948 and 1972. It was estimated that this study group constituted about 70% of all the pesticide workers in the GDR from that time period. Causes of death and diagnoses of cancer were obtained from death certificates and from tumor reference centers. The expected number of tumors was obtained for five-year age classes based on published age and sex specific rates for 1973. Of 169 tumors, 59 were bronchial carcinoma (tumors of trachea, bronchus or lung). Standardized Mortality Ratios (SMR)^α were calculated for age-specific groups from 1970 to 1978 giving a 2.1-fold average increase in risk for lung cancer. As with the earlier paper, this analysis would have been improved by using person-years of observation since it is not known whether all the men were observed from 1970 to 1978. Furthermore, the expected number for SMR analysis was calculated for only 8 years, not 9 (1970-78), which gives a erroneously high value for the SMR.

Smoking status of the workers was estimated by comparing the smoking habits of a sample of workers with those of a "random" sample of men from the general public who were attending an x-ray examination. Smoking was shown not to be a likely explanation for the cancer cases.

^α Standardized Mortality Ratio is the ratio of observed number of cases of disease, deaths, etc. in the study population to the expected number of cases. The expected number of cases is calculated from the rate of the disease, deaths, etc. in a standard or control population times the number of persons or person-years in the study population.

However, since the workers were exposed to a large variety of chemicals, it is impossible to know what effects could be due to 2,4-D formulations alone; therefore we will not include this study in our analysis. If only a few chemical compounds had been common to this heterogeneous group of industrial products, the task of focusing on the probable causative agent would be enormously facilitated.

Another example of the problems of a large cohort study is shown by the report of Morgan et al. (1980). The purpose of the study was to examine the health status of 3669 volunteers from 1971-1973, 2620 of whom were occupationally exposed to pesticides. Very little can be concluded from the study because of the difficulty in defining exposure, the use of unmatched controls and most of all, because there was only a 75% follow-up of original subjects.

Riihimäki et al. (1982) published a first report on an ongoing study of a cohort of herbicide applicators (N = 1971). In most cases, the exposure was of short duration, poorly documented and very recent. For all types of cancers and mortalities examined, using 10- and 15-year latency periods, the number of observed cases was less than the expected for any of the causes. Because the history of past exposure is imprecise, the authors warn that the results should be interpreted with caution. More recently, Riihimäki et al. (1983) published a supplementary report with data on cancer morbidity. In an examination of cancer morbidity from 1972-1978, taking into account a 10-year latency period, no significant differences were found between the observed and expected number of cancers. It must be stressed that all the limitations in Riihimäki et al. (1982) also apply to this report.

5.1.3 CASE-CONTROL STUDIES

A series of three case-control studies was carried out by Hardell and coworkers in Sweden. Hardell and Sandstrom (1979) investigated 52 male patients from northern Sweden who were admitted to the Umeå hospital with a diagnosis of soft-tissue sarcoma (a relatively rare disease). For each of the 21 living cases, four controls were chosen from the national population registry and were matched for sex, age and place of residence. For the 31 deceased cases, controls were chosen from the national registry of deaths and were matched for sex, age, date of death and residence. The working status, present or former, of the controls was verified. Exposure to phenoxyacids or chlorophenols was assessed by means of questionnaires to living cases and controls and to relatives of deceased subjects. Questions were asked about previous or present occupation and possible exposures to chemicals. Further confirmatory information was obtained by contacting employers to verify use of particular chemicals. The statistically significant findings are seen in Table 5-1. The risk ratio for soft-tissue sarcomas after exposure to phenoxyacids was 5.3 (2.4-11.5, 95% confidence interval).

Eriksson et al. (1981) investigated the relationship between soft-tissue sarcoma and exposure to phenoxyacids or chlorophenols for patients who lived in the south of Sweden. There were 110 cases and 220 controls matched for age, year of death and residence. The results were similar to those of the first study. A separate analysis was carried out for "non-2,4,5-T" phenoxyacids (i.e. 2,4-D, 4-chloro-2-methyl phenoxyacetic acid (MCPA), mecoprop and dichlorprop). There was a significant risk for soft-tissue sarcoma after exposure to these phenoxyacids; the risk ratio was 4.2 (95% confidence interval calculated by Coggon and Acheson (1982), 1.2-14.9).

Hardell et al. (1981) examined a different cancer, malignant lymphoma, and previous exposure to phenoxyacids or chlorophenols. There were 169 cases and 338 matched controls. As in the previous studies, there was a significant risk of malignant lymphoma after exposure to these chemicals, the risk ratio being 4.8 (2.8-8.1, 95% confidence interval). Hardell et al. (1981) concluded that exposure to phenoxyacids or chlorophenols, as well as to organic solvents, constitutes a risk of developing soft-tissue sarcoma and malignant lymphoma and the risk is related not only to 2,4,5-T, but also to other phenoxyacids.

The major criticism that some apply to the Swedish case-control studies pertains to the statistical analysis. The control subjects were individually chosen to match a case and, while the odds ratio was initially calculated based on a matched sample, it was then subsequently calculated as if the controls had been chosen as a group rather than individually, i.e. "unmatched". However, this would in fact underestimate the statistical significance since the unmatched analysis gives a lower odds ratio. It is also very important to note the similarity of the magnitude of the effect (RR = 5.3, 4.8, 4.2) found in these studies. This substantially enhances our confidence in these results.

Two recent studies by these authors (Hardell 1981; Hardell et al. 1982) support the validity of their earlier results. Hardell (1981) used the same case-control methodology and found no relationship between exposure to phenoxyacids or chlorophenols and cancer of the colon, nose or nasopharynx. This "negative" finding tends to rule out the possibility of a systematic error in regard to the ascertainment of exposure or occupation in the first three studies.

Hardell et al. (1982) found no relationship between cancer of the nasopharynx and exposure to phenoxyacids (see Table 5-1). They used a case-control methodology but utilized the data for the controls from their earlier studies. Although the authors might be criticized for not using "fresh" controls, they found that the controls were similar to the cases in terms of residence and stratified the analysis by age and vital status in determining the odds ratio. Furthermore, it is unlikely that a bias was introduced while collecting exposure data for the cases since ascertainment of exposure was done at the same time as the colon cancer

study, and researchers did not know who were cases of cancer and who were controls. Thus, a relationship between phenoxyacids and cancer was not found for all types of cancer studies.

Hardell's works is not accepted by all scientists and it has been heavily criticized for its study design (i.e. obtaining exposure information from relatives), interpretation (Lamm 1982) and on the basis of disease identification (Rawls 1983). Diseases such as soft-tissue sarcomas are a rare type of cancer and since most pathologists have very little experience in identifying them, medical records may be inaccurate (Rawls 1983). The involvement of experienced pathologists in epidemiological studies would greatly enhance the confidence in the diagnoses (Campbell 1983).

A case-control study on soft-tissue sarcomas in New Zealand was conducted by Smith et al. (1983). An assessment of these cancer patients and their exposure to phenoxy herbicides gave a relative risk of 1.7 for those patients with at least one day's exposure (not in the last 5 years before the reporting of cancer) to phenoxy herbicides. While this is not statistically significant and much weaker than the relative risk found in the Swedish studies, it is in the same direction. One puzzling result of the study is that no cases were found among pesticide sprayers, probably the most highly exposed group. This is indirect negative evidence though, and it is uncertain how much weight it should be given. Little confidence can be placed in all these results because of the ill-defined and short exposure. The exposure was stated only as greater than 1 day or less than 5, and also it was not always known to what chemicals the workers were exposed.

Cantor (1982) reported on a case-control mortality study using mortality listings for male residents of Wisconsin (USA) for the years 1968-76. There were 774 cases of non-Hodgkins lymphoma (NHL) death and 1651 matched controls. Information on occupation was obtained from death certificates; farmers were defined as owners, tenants or foremen. Farm laborers were excluded from the exposed group and classified as unexposed because it had been demonstrated (Milham 1976) that their patterns of mortality differ from those of the other farmer groups. It is not clear whether this may have caused distortion or introduced a bias in the study. Additional indices of the intensity of exposure were calculated on the basis of area statistics on farm-related activities. The results (Table 5-1) show that farming was more common among cases than among controls: odds ratio (OR) = 1.2. NHL Death occurring before age 65 (OR = 1.7) and among these, reticulum cell sarcoma (RCS) deaths (OR = 2.7) was more common in farmers than in controls. This was not the case in farmers older than 65 years. The strength of this association increased over the 3-year periods of the study for all 3 cell types of NHL examined. The ORs for all NHL increased from 1.2 (1969-70) to 1.7 (1971-73) to 2.1 (1974-76). County classifications of the type of farming and other agricultural characteristics were used to calculate area indices of the intensity of exposure. The associations found were limited to reticulum cell sarcoma (age < 65) with odds ratios

ranging from 1.7 to 6.6 for pesticide use and small grain or wheat farming.

It is not known exactly which pesticides were used in Wisconsin, but chlorinated phenoxyacids are widely used in the U.S. as herbicides in corn and wheat production (US Dept. of Agriculture 1968). Cantor (1982) points out that the trend in risk of reticulum cell sarcoma and lymphosarcoma in farmers during 1968-76 suggests a relationship with exposures that commenced about 20 years earlier. Phenoxy herbicides, as well as many other agriculture chemicals (i.e. dieldrin, DDT, aldrin, chlordane etc.), could be involved since they all came on the market in large quantities in the late 1940s and early 1950s.

These types of studies, which are based on routine vital statistic records and use data for the control group from relatively large geographic areas, lack precision, particularly in the assessment of exposure. For example, occupational information stated on death certificates often only reflects the last known job and is at times uninterpretable, i.e. retired, Government employee, and laborer. As well, indices of exposure calculated from area statistics are only an indirect indication of the type of exposure suffered by the individuals. It is therefore safe to conclude only that the results, in general, support the hypothesis of an association between reticulum cell sarcoma in males less than 65 years old and insecticide and pesticide use.

5.1.4 SHORT COMMUNICATIONS

5.1.4.1 Carcinogenic Effects

A review of the reports associating phenoxy herbicides and cancer in man (Coggon and Acheson 1982) inspired an editorial by The Lancet as well as several letters from involved or interested scientists.

The editorial (Lancet 1982) reviews the evidence for soft-tissue sarcomas in addition to pointing out the inherent difficulties in interpreting retrospective investigations. Suggestions for improving measurements of exposure by measuring various parameters of body burden (plasma, urine, etc.) are mentioned. It is also indicated that a better description of the histological and clinical features of the particularly rare type of tumor involved (soft-tissue sarcoma) may indicate stronger characteristic patterns in terms of age distribution, anatomical sites and clinical features. This in turn, may strengthen the etiological association.

Hay's (1982) response to the editorial deals with the mutagenic properties of dioxin isomers, including those found in 2,4-D formulations, and indicates the relatively varied morphological types of

cancer that have been induced in animal experimentation. He stresses that the link between 2,4,5-T and soft-tissue cancer should remain under scrutiny but that other chlorinated herbicides should be looked at as well.

Milham (1982) disputes the association between phenoxy herbicides and cancer discussed in Coggon and Acheson (1982). He reports on an update of an occupational mortality study conducted in Washington State. Mortality due to soft-tissue sarcoma, Hodgkin's disease, lymphosarcoma and other lymphomas is compared for the various occupations with exposure to phenoxy herbicides and chlorophenols. Significant excesses of soft-tissue sarcoma and Hodgkin's disease were found in farmers and paper makers respectively. The authors also point out that these two occupations do not appear among the 15 occupations with the highest proportional mortality rates (PMR)^α for soft-tissue sarcoma in the state.

Sarma and Jacobs (1982) reported three cases of soft-tissue sarcoma that have occurred in veterans who served in Vietnam and were exposed to Agent Orange (50:50 combination of 2,4,5-T and 2,4-D) as well as other defoliants. Based on the rarity of soft-tissue sarcoma as well as on a possible prevalence of these neoplasms in Vietnam veterans, Sarma and Jacobs (1982) questioned whether the defoliants, another environmental factor, or perhaps a combination of factors are the cause of this association.

5.1.4.2 Reproductive Effects

As there have been very few actual epidemiological studies on the reproductive effects of 2,4-D, most of our information comes from reports of congenital abnormalities that may be associated with Agent Orange or other herbicides.

In Australia (Anon 1978; Lee 1978), New Zealand (N. Z. Department of Health 1977) and Oregon, U.S.A. (Hatch and Kline 1981), several clusters of birth deformities have been suspected of being associated with phenoxy herbicides. In all cases, official enquiries showed no definitive evidence linking the infant malformations with the use of herbicides. It is however extremely difficult to investigate relatively small clusters of adverse reproductive effects. First it must be shown that an unusual cluster has indeed occurred and the multitude of confounding variables that can effect the incidence of reproductive effects must then be considered. These variables may

^α The proportional mortality rate is the number of deaths due to a particular disease divided by the total number of deaths in a given time period.

include genetic factors, demographic data (age, birth order), life style habits (smoking, drinking, drug abuse) and even the therapeutic use of medication. These difficulties notwithstanding, repeated occurrence of anecdotal evidence should be treated seriously by the scientific community as they indicate the need for additional surveillance.

Recently, the Australian reports were reviewed by Hall and Selinger (1980; 1981). The authors indicate that there has been a definite increase in mortality from congenital abnormalities over the period 1960-1977 in the Yarram District of Victoria, as compared to the whole State of Victoria. Although this increase appears to be consistent with the introduction of Agent Orange in Australia and its use in that district, the authors state that there is no clear evidence linking the trend with the usage of herbicides. It must also be noted that the largest increase (between 1975 and 1977) is based on only four reported deaths from congenital abnormalities.

Owing to concern over the use of Agent Orange at Camp Gagetown, New Brunswick, in 1966 and 1967, a study of vital statistics and hospital morbidity data for Sunbury County, N.B., was conducted (Wigle and Mao 1981). Although the study showed no significant increase of adverse pregnancy outcomes, the lack of exposure data precludes any conclusions about the effects (or lack thereof) due to the use of defoliants.

The effects of the use of Agent Orange in Vietnam in the mid to late 1960's was the topic of an international conference in Vietnam in January 1983 (SIPRI 1983). While no complete reports are available, the working groups indicated that retrospective studies were presently being carried out to determine if the indications of reproductive effects are real.

A report of a possible mutagenic effect from Agent Orange comes from a study of chromosome abnormalities conducted in Chicago, Illinois (Rao *et al.* 1980), which showed a statistically significant increase in chromosomal breaks in the exposed males. Of the 10 families studied, eight had one or more children with birth defects. Exposure history was not reported. As only the abstract of this study was available, further analysis cannot be carried out. Linnainmaa (1983) tested for mutagenicity by studying the induction of sister chromatid exchanges in the peripheral lymphocytes of forestry workers spraying 2,4-D and MCPA in Finland. No effect was found at urinary concentrations as high as $10.02 \mu\text{g.mL}^{-1}$ 2,4-D and $1.14 \mu\text{g.mL}^{-1}$ MCPA. However, Korte and Jalal (1982) did find a significant increase in the sister chromatid exchange rate in human lymphocytes treated in vitro with 2,4-D at $10 \mu\text{g.mL}^{-1}$ or higher.

5.2 ESTABLISHING CAUSAL RELATIONSHIPS

Scientists and the public alike are interested in knowing whether a given chemical or substance is the cause of some adverse

health outcome, e.g. cancer. Providing support for a cause and effect relationship between a given chemical and a given disease is an extremely difficult task. Using the available epidemiological methodologies, it is impossible to prove such a relationship beyond all doubt. Instead, one must weight all the evidence in perspective before developing a judgment.

In epidemiology, most erroneous positive or negative associations stem from improperly designed or improperly conducted studies, so the first step is to ascertain that there are no methodological flaws.

Statistical significance is only one element in the process of assessing causation; even if the association observed did not reach acceptable levels of statistical significance, the trends should be noted (Cole 1979). These trends can, at the very least, indicate what direction further studies should take.

If it is concluded that the association found is a "true" one, it must be decided, with a reasonable degree of confidence, whether or not the association indicates a cause-effect relationship. Lacking the confirmatory evidence from experimental studies conducted on a human population, generally an unacceptable approach, it cannot be determined that a given association is, unequivocally, a causal one.

5.2.1 HILL'S CRITERIA FOR CAUSAL RELATIONSHIPS

Hill (1965) originally formulated a number of guidelines that have, with the contributions of other investigators, become of standard usage among researchers. To arrive at a well reasoned judgment it is not necessary that all of the conditions be met, but the more that are found to be true, the greater the likelihood that the proposed association is a causal one.

The criteria, as outlined below, should be kept in mind in interpreting epidemiologic data arising from a number of studies when one is using these studies to set standards. These guidelines have been used for our analysis of the epidemiological studies on 2,4-D formulations (Table 5-2).

5.2.1.1 Consistency

In epidemiologic studies, where the control of environmental variables is often impossible, an association consistently found by different researchers and research methodologies is much more impressive than an association which is inconsistent from one study to another. In the 2,4-D studies there are consistencies between the three case-control studies by Hardell's group (Hardell and Sandstrom 1979; Hardell et al.

Table 5-2. Guidelines to assess causal relationships.

Guidelines	Evidence for 2,4-D
1. Is the association consistent?	Hardell and Sandstrom (1979); Hardell <u>et al.</u> (1981); Eriksson <u>et al.</u> (1981) had similar risk ratios in retrospective studies in Sweden. Axelsson <u>et al.</u> (1980): significant findings in an historical prospective study in Sweden. Riihimaki <u>et al.</u> (1982): no association in an historical prospective study in Finland.
2. Strength of association	Axelsson <u>et al.</u> (1980): risk ratio: stomach cancer and phenoxyacids = 3.1. Hardell and Sandstrom (1979): risk ratio for soft-tissue sarcomas after exposure to phenoxyacids = 5.3 (2.4 - 11.5). Eriksson <u>et al.</u> (1981): risk ratio for soft-tissue sarcoma after exposure to phenoxyacids = 5.1 (2.5 - 10.4). Hardell <u>et al.</u> (1981): risk ratio for malignant lymphoma after exposure to phenoxyacids = 4.8.
3. Dose-response relationship	Hardell <u>et al.</u> (1981): exposure to PHA < 90 days; risk ratio = 4.3; exposure to PHA > 90 days; risk ratio = 7.0.
4. Does the association make biological sense?	A dose-related occurrence of tumors has been reported in animal studies (Hansen <u>et al.</u> 1971).
5. Temporal relationship	Exposure to 2,4-D occurred before onset of carcinoma. Latency period of 10-20 years is consistent with that expected for carcinoma (Hardell 1981).
6. Is the association specific?	Agent is suspected of causing carcinoma of lung, malignant lymphoma, soft-tissue sarcoma and stomach cancer. It would be difficult to explain this variation by a single specific mechanism, but it could be consistent with a general mechanism affecting all systems. However, there was no association with cancer of the colon.

1981; Eriksson et al. 1981) in terms of results found and in the magnitude of the odds ratios. The findings of Axelson et al. (1980) also support this. In contrast, Riihimaki et al. (1982) did not find any increased risk from herbicide exposure although the period of reported exposure was often very short (minimum of two weeks).

5.2.1.2 Strength of Association

Associations showing high relative risk (or odds ratio), particularly if they are of a constant magnitude, are less likely to be due to confounding variables. The previously mentioned magnitude of OR (range 3.1-5.3) between phenoxy herbicides and carcinoma indicates a very strong relationship.

5.2.1.3 Dose-Response Relationship

While the lack of a distinct dose-response relationship (linear or not) cannot be construed as evidence against causality in human population studies, the finding of such a relationship argues strongly for a cause-effect relationship. Misclassification and the variability of measurements can be responsible for the lack of increase in response following an increase in exposure. For 2,4-D, only the study by Hardell (1981) indicates a dose-response relationship.

5.2.1.4 Biological Plausibility

Coherence between animal experimentation and human findings obviously favors causality. While there are few other reports of carcinogenicity related to phenoxy herbicides, Hansen et al. (1971) reported tumorigenicity in rats treated with 2,4-D. In a 2-year feeding study with the rats receiving up to 1250 mg (2,4-D).kg-diet⁻¹, there was a dose-related statistically significant increase in the proportion of females with tumors, and males with malignant tumors with increasing log 2,4-D dosage. The tumor types were randomly distributed and of the type normally found in aging Osborne-Mendel rats, did not indicate target organs and the mortality rates were not affected. While a description of the problems of extrapolating from animal experiments to humans is beyond the scope of this review, it is worth pointing out that a substance which causes cancer in a certain species will not necessarily do so in humans.

For an association to be believable it should be explainable by a biologic (physiopathogenetic) mechanism of action. As with epidemiological studies, Hansen et al. (1971) found no common specific target site albeit this would be consistent with the role of 2,4-D as a promoter rather than a primary tumorigen. The biggest limitation here lies in the inadequacy of knowledge. Evolving clinical and toxicological concepts should always be considered.

Another important point is the presence of dioxins and other contaminants in the formulated products of 2,4-D. While the most toxic dioxin isomer known, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, is not present in 2,4-D, other isomers are found (See Chapter 2.0). Since all the dioxin isomers that have been properly tested have been shown to be carcinogenic, it is plausible that the dioxins in 2,4-D may be a cause of its "supposed" carcinogenicity.

5.2.1.5 Time Relationship

There appears to be little doubt from the examination of 2,4-D studies that exposure preceded the induction of cancer. Of particular importance is the demonstration of a long latency period in the Hardell (1981) study.

5.2.1.6 Specificity

The finding that the relationship between phenoxyacids and carcinoma involves different types of carcinoma argues against specificity of effects by a single mechanism, although it may be a general mechanism effecting all systems. It could also be that phenoxys are actually secondary carcinogens and work by suppressing the immune systems or the mixed function oxidase (MFO) system. However, the relationship does not hold for carcinoma of the colon, nor for nasal or nasopharyngeal carcinoma.

As to specificity of cause, one of the striking features of this analysis is that, in all the investigations, the study subjects were exposed to more than one chemical and in particular to more than one phenoxyacid. Many were exposed to 2,4,5-T, which is likely to be contaminated with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. There was no possibility for separate analyses for the effects of 2,4-D alone. Even if the studies could be limited to examining the effect of only 2,4-D, the variations in the formulations would have to be considered. There are a multitude of 2,4-D formulations and each one may have different levels and combinations of dioxins and contaminants. A study can only make conclusions for the single formulation examined. Therefore, alternative explanations still exist for the findings in all the studies; that is, the cancers could have been caused by factors other than, or in addition to, 2,4-D.

5.3 INDICATIONS FOR FURTHER STUDIES

Future studies, whenever possible, should attempt to focus on differential exposures to one chemical. Furthermore, the investigator must consider the role of other components of the formulation such as solvents and emulsifiers and contaminants of the

active product as possible carcinogens. This is an extremely difficult task. Answers will best be obtained by refining the hypothesis and resisting the temptation to try to answer too many questions at once.

Table 5-3 lists proposed studies which could enhance our understanding of the health effects of 2,4-D. Health effects other than cancer are also of interest. All the studies proposed would be expensive and difficult to carry out. As with studies already done, the greatest difficulty would be in determining exposure history. Since cancer has such a long latency period, monitoring adverse reproductive events has the advantage that the adverse events can be recognized in a very short period of time.

In conclusion, there is some evidence to suggest an association between various cancers and phenoxyacids. However, there is no evidence supporting the relationship for 2,4-D alone because none of the studies have been adequately controlled for confounding factors.

Table 5-3. Possible future studies on 2,4-D in Canada.

	Description	Advantages	Disadvantages
1. CANCER STUDIES			
A) Observational studies			
i) Cross-sectional	Compare rates of soft-tissue sarcomas between an area where 2,4-D has been used and an area where it has not been used.	Relatively inexpensive.	Difficult to find regions where 2,4-D is not used because of widespread domestic availability. Too many other variables might account for any differences which might be found.
ii) Longitudinal	Obtain list of farmers (e.g. from agricultural survey) and establish computer record linkage with cancer registries and death certificate computer files with list of farmers.	Relatively inexpensive.	Very dependent on availability and quality of data. Many persons would be lost to followup, so initially many persons would have to be included. Also difficult to obtain exposure data from records.
(iii) Cohort (Prospective)	Follow a group of farmers or sprayers for 10-20 years by regular questionnaires, physical examinations and lab tests to determine health outcomes. Use another occupational group as the nonexposed.	Can get more accurate exposure data.	Very expensive. Must study large numbers of persons as the development of soft-tissue sarcoma is rare and many persons are lost to followup. Still would have the problem of exposure to several chemicals.
(iv) Historical Prospective	Obtain list of farmers, sprayers from 10-20 years ago. Check cancer registries/death certificates to determine any cases of soft-tissue sarcomas. Compare with another occupational group.	Less expensive than cohort study.	Very dependent on availability of data. Difficult to get accurate exposure data from 10-20 years ago. Too many confounding variables could account for differences.
(v) Case-control (Retrospective)	Check cancer registries/death certificates for cases of lymphoma/soft-tissue sarcoma. Use another disease category (e.g. accidents) as a control group. Determine exposure to herbicides or occupational status most likely to have used herbicides by record linkage or contacting individuals or their families.	Less expensive and may be more feasible to carry out than prospective study.	May not be sufficient cases of soft-tissue sarcoma in Canada. Difficult to obtain accurate exposure data especially if more than one chemical has been used.
B) Intervention studies	Randomly assign individuals or communities to receive exposure to 2,4-D or a placebo.	Conclusions from experimental studies are the most valid.	Not ethical on humans - animal studies only.
2. REPRODUCTIVE STUDIES			
Observational studies			
i) Cross-sectional	Compare rates of congenital anomalies, spontaneous abortions, and chromosomal abnormalities in persons who live in areas heavily sprayed with 2,4-D (e.g. farmers) and compare results with those from areas not using 2,4-D.	Latency period is much shorter than for cancer.	May be difficult to find areas where 2,4-D is not used. Methodology for this type of study is very expensive and controversial. Interpretation of outcome measures, e.g. chromosomal abnormalities, is still subject to debate.
(ii) Longitudinal	Follow exposed group with respect to adverse pregnancy outcomes. Use of control group would be desirable.	Same.	Same.
3. ASSESSMENT OF RISK OR EXPOSURE			
	Measurement of body burden (blood, urine or tissue) of specific chemicals after known exposure.	Easy definition of intensity and specificity of exposure	

APPENDIX I.0 A COMPUTER MODEL FOR THE DRIFT AND DEPOSITION OF AN AERIAL HERBICIDE IN AGRICULTURE

I.1 USE IN AN AGRICULTURAL SCENARIO

The computer model used in the NRCC aminocarb document (NRCC 1982) to predict exposure to aminocarb in a forest scenario has been modified to simulate the situation with 2,4-D in an agricultural scenario. The model is two-dimensional in (x-z) coordinates with x measured horizontally from the flight line and z vertically from the ground. As was the case in the forest-spray-drift computations (NRCC 1982), the situation in the y-direction, parallel to the flight line, is assumed to be homogeneous. This requires that the spray swath be longer than the downwind distances of interest since end effects are not considered in the model. Model-predicted exposures of 800 m, therefore, may err on the conservative side inasmuch as few aerial spray swaths in agriculture are longer than 800 m.

I.2 MODEL STRUCTURE

In order to be used for an agricultural situation, the model had to be adapted to the much narrower spray swath. Considering that the dominant streamwise length scale of the vertical fluctuating wind, w, the most important turbulence component in this problem of droplet drift and deposition, is of the order of z in both cases, it is apparent that the considerable spatial averaging possible in the forest case is not available in the agricultural case. Thus, the gradient-transfer hypothesis (K-theory) is not likely to be successful. Instead, individual droplet trajectories are computed for cases of the weakly turbulent atmospheres characterizing aerial spray practice.

In the present computations, the turbulent motion of the spray droplets is modelled as in Reid (1978), Legg and Raupach (1982) and Ley (1982). However, the model extends these calculations to evaporating droplets having non-zero terminal velocity. A statistically significant number of droplets is subjected to a series of random walks with a small time step compared with the Lagrangian integral time scale of w:

$$T_L = \int_0^{\infty} \frac{\overline{w(t)w(t+\tau)}}{\sigma_w^2} d\tau \quad (1)$$

in which t is time, τ is time 'lag', σ_w is the root mean square (rms) value of w and the overbar denotes an ensemble average. For time much greater than T_L , it is possible to define an asymptotic vertical eddy diffusivity by

$$K = \sigma_w^2 T_L \quad (2)$$

which is the basis of the K-theory used in the forest spray drift model (see NRCC 1982).

An alternative specification of K from atmospheric surface-layer theory is

$$K = k u_* z / \phi_h \quad (3)$$

in which k is the Von Karman constant $= 0.35$, u_* is the friction velocity $= \sqrt{-u'w'}$ where u is the turbulent component of longitudinal wind and ϕ_h is the normalized vertical temperature gradient. In neutral flow (the case considered in the present computations) $\phi_h = 0.74$ and $\sigma_w = 1.25u_*$ so that the equation for T_L in the present model is

$$T_L(z) = 0.4z / \sigma_w \quad (4)$$

Typical values of T_L in the atmospheric surface layer follow from typical values of σ_w and z equal, say, to 40 cm.s^{-1} and 10 m respectively. These values yield $T_L = 10 \text{ s}$. The streamwise integral length scale corresponding to T_L is

$$l(z) \approx U(z) T_L(z) \quad (5)$$

in which $U(z)$ is mean wind speed. A typical value of U is 3 m.s^{-1} giving $l \approx 30 \text{ m}$ which, although short compared to the initial cloud width in the forest spray model, exceeds the initial width of the spray cloud from an agricultural spray plane. Thus, whereas K -theory was valid in the forest spray drift model, the present problem requires computation of individual droplet trajectories. The above argument holds for any wind speed inasmuch as a doubling of U doubles σ_w but halves T_L leaving $l(z)$ unchanged.

The spray droplets also respond to the longitudinal and lateral turbulence velocities, u and v . The latter are ignored in these calculations on the assumption of homogeneity in the crosswind direction. The former are included although their net effect on droplet motion is small since u is small relative to the mean longitudinal wind, $U(z)$.

1.3 INITIAL CONFIGURATION OF THE DROPLET DRIFT CLOUD

Wind tunnel studies at NASA's Langley research facility (Jordan et al. 1978) reveal a characteristic three-node cross section of the droplet cloud generated by an agricultural spray plane flying within a semi-wingspan of the ground. The weaker central node results from the propeller wash. The outer two dominant nodes result from droplets entrained into the wingtip vortices and carried 5-6 m aloft by vortex rebound. The same study reveals that for the unit density droplets of these computations, the loss of droplets to the vortices depends on the spanwise position of the atomizing nozzle. Thus, droplets $200 \mu\text{m}$ in diameter are the largest that are entrained from an outboard nozzle

whereas droplets 100 μm in diameter are the largest entrained from a mid-span nozzle. Droplets smaller than 50 μm in diameter are assumed in these computations to be entrained from all nozzle locations.

These droplet source details are modelled in the present computations since they influence the fraction of the chemical emission subject to wind drift from an aerial agricultural spray swath. The initial drift cloud in this paper is assumed to be 18 m wide and extend from 1 m agl to 6 m agl. Of this area, two blocks, each 4 m high and 3 m wide and located symmetrically with respect to the middle of the cloud between 2 and 6 m agl, contain no droplets. The remaining cross-sectional area contains three humps representing the two wingtip vortices and the propellor wash vortex.

I.4 INITIAL NUMBER DENSITY OF DROPLETS IN THE DRIFT CLOUD

For this monograph, the model is used to simulate two Canadian situations involving the spraying of 2,4-D. The first scenario is the aerial application of 2,4-D on a field in the Prairies and the second is an aerial spray of a 2,4-D/2,4,5-T mixture on a tree plantation in New Brunswick. As different spray nozzles are used in each scenario, droplet size and number distributions from each are considered.

- 1) the hydraulic D6-46 nozzle emission measured by Akesson and Yates (1981) with a laser probe which is assumed to be representative of spray emissions on the Canadian Prairies, and
- 2) the flat fan Teejet nozzle emission recently measured by Picot (1983) using a laser spectrometer ^{α} , which is assumed to be representative of spray emissions in Eastern Canada. Although the 11010 Teejet has been observed to generate smaller droplets than the 8000 series used on agricultural spray planes (Tomney *et al.* 1978), the presence of low ambient temperature accompanying Picot's test should bring the two size distributions closer together. As an approximation to the true distribution, Picot's data are used unaltered in the absence of more detailed information on the droplet-size distributions from the 8000 series agricultural Teejets.

To set the initial numbers of droplets in the drift cloud, a swath interval of 15 m is assumed which yields 42 mL of formulation per metre of flight line on the Prairies and 56 mL per metre in Eastern Canada. Based on their water content, the evaporated droplet diameter

^{α} Picot's measurements were made at a temperature of -6°C in the NRC VTOL tunnel using a 11010 Teejet and a weak aqueous formulation of deicing fluid.

would be 42% of the initial diameter on the Prairies and 38% in Eastern Canada. As an approximation, the model computation of evaporation was terminated when the diameter equalled 45% of its initial value inasmuch as some small residue of water is expected to remain with each droplet (Sundaram 1983). A mean droplet density of 1.05 g.mL^{-1} is adopted. Table I-1 lists the numbers (per size range) from each nozzle per 80 cm of flight line (80 cm is the width of the bystander targets downwind). In both cases, the droplet distributions extend beyond 200 μm in diameter but as noted earlier, these sizes are not susceptible to wind drift.

The tabulated numbers of droplets refer to the situation resulting from the atomization process. As explained earlier, not all enter the drift cloud created by the wingtip vortices and propeller wash. Thus the 200 μm diameter droplets are arbitrarily assigned a weight of 0.1, i.e. the ratio of 2 outboard atomizing nozzles to ≈ 20 overall, the 166.7- μm -diameter droplets a weight of 0.2, the 133.3- μm -diameter droplets a weight of 0.5, the 66.7- μm -diameter droplets a weight of 0.8, and all others a weight of unity.

I.5 EFFECT OF SPRAY PLANE VORTICES ON DRIFT CLOUD BEHAVIOR

When the droplets enter the wingtip and propeller vortices, their paths are essentially the resultant of the mean wind, the circulation of the vortices and their terminal velocities (Wickens 1980). However, because of non-conservative frictional stresses between the vortex flows and the ground, the circulation is steadily eroded and eventually the droplet motion is controlled by mean wind, gravity and atmospheric turbulence. In the present model the life time of the vortices is assumed to be $\approx 30 \text{ s}$ during which time the effect of atmospheric turbulence is assumed to increase steadily from zero to unity.

I.6 MODEL RESULTS

The dermal, oral and inhalation exposures from a single spray swath are tabulated in Section 4.3.1 (Tables 4-1 and 4-2) for all droplet size classes. Trajectories of 9800 individual droplets in each size class were computed to generate the tabulated results. In each case, the computer predictions were scaled up from the number of droplets analyzed, to the actual number existing in the size class.

Table I-1. Numbers and velocities of the droplets in the drift cloud resulting from the D6-46 and Teejet nozzles.

Initial Droplet Diameter (mid) (μm)	Terminal Velocity V_{SI}^{α} (cm.s^{-1})	Evaporated Diameter (μm)	Terminal Velocity V_{SE}^{β} (cm.s^{-1})	Number of Droplets	
				D6-46 Nozzle	Teejet Nozzle
12.5 (0-25)	0.49	5.6	0.10	1×10^5	3.45×10^9
37.5 (25-50)	4.35	16.9	0.90	1.10×10^5	6.47×10^8
66.7 (50-83.3)	13.60	30.0	2.84	4.96×10^4	1.49×10^7
100.0 (83.3-116.7)	26.80	45.0	6.38	3.99×10^4	7.36×10^6
133.3 (116.7-150)	42.10	60.0	10.77	4.34×10^4	3.27×10^6
166.7 (150-183.3)	58.10	75.0	16.40	1.18×10^5	1.29×10^6
200.0 (183.3-215.7)	72.60	90.0	22.48	2.10×10^5	8.17×10^5

$^{\alpha}$ V_{SI} = Terminal velocity of the initial droplets.

$^{\beta}$ V_{SE} = Terminal velocity of the evaporated droplets.

APPENDIX II.0

AN INTRODUCTION TO THE SCIENCE OF EPIDEMIOLOGY

In this Appendix, some important epidemiology concepts will be discussed and the epidemiological basis for defining a chemical as the cause of a particular health outcome will be explained. This is not intended to be a substitute for formal textbooks in epidemiology (see MacMahon and Pugh 1970; Mausner and Bahn 1974; Friedman 1980). Rather, it is meant to help the reader understand some of the difficulties researchers face in assessing the safety of the ever increasing number of potentially toxic chemicals used in modern industry. One must recognize these difficulties before an informed evaluation can be made of any epidemiological study.

II.1 OCCUPATIONAL EPIDEMIOLOGY

Occupational epidemiology considers possible associations between various occupational exposures and diseases. Investigations of such associations are complicated by the fact that the exposures are often ongoing or may have happened several years ago. Furthermore, the disease may have a long latency period. This contrasts with occupational medicine which generally deals with acute illnesses that occur after known exposures to toxic substances at the work place. In the work place, the association is usually self-evident since both the toxic agent and its effects are often well known.

Recently, attention has been focused upon the need to explore the relationship between long-term health effects and long-term exposures to low levels of toxic substances. Often it is unclear which substance may be involved, let alone what kind of effect is expected. Epidemiological studies are prompted by results from animal experiments, indications from chemically similar substances and from observations of clusters of some serious adverse health effects such as cancer or reproductive failures. In most instances there is little or no immediate effect and the disease may not develop until after the individual has changed jobs several times.

Very seldom are individuals exposed to a single chemical substance at a time. To study multiple chemical exposure properly, traditional epidemiological techniques taken from chronic disease epidemiology have had to be adapted. Still, epidemiologic methods are not as precise as those used in toxicology. Their value lies in their capability of detecting group effects in human populations which can lead to more specific toxicological studies. In trying to deduce the effects of a given chemical, the epidemiologist does not have the same experimental conditions for humans as the toxicologist has for animals. The toxicologist can control factors such as environment, diet and compliance of the subjects, which allows the effects of varying the dose and individual biological differences to be studied factor by factor in order to identify causative relations. The epidemiologist, however,

usually does not have the same level of control on such factors and therefore tends to rely heavily (but not exclusively) on statistical methodologies which permit him to better understand the probability of specific associations with a given disease.

II.1.1 BASIC MEASUREMENTS

II.1.1.1 Measuring the Frequency of Events

The first step in exploring a relationship between an adverse health outcome and exposure to a chemical is to look at the frequency at which diseases develop in an exposed population. For epidemiologists, the basic way to monitor the frequency of a given event is to calculate the "rate" at which the events (e.g. the number of cancers) have occurred in a population at risk (e.g. workers in a specific industry).

Two commonly used rates in epidemiology are the prevalence rate and the incidence rate. The prevalence rate is expressed by the number of cases of a disease present in a given population at a given time (or within a period of time). The incidence rate, or cumulative incidence, is expressed by the number of persons developing the disease in a population at risk in a given time.

Incidence rates therefore require the study of a population, initially free of disease, over a period of time to note the frequency at which the disease develops within that population. This implies setting up a study that monitors events for several years into the future. Most frequently, however, a situation exists wherein the formation of an exposure group of workers has occurred in the past. Their experience would then be followed up to the present.

Rates can be refined to measure different parameters; they can be age-specific, sex-specific or cause-specific. When dealing with the frequency of death rather than of disease, "crude" and/or "specific" mortality rates are used. One particular type is the case-fatality rate (number of deaths from a specific disease divided by the total number of cases of the same disease) which measures the lethal effect of a given disease.

To determine whether the frequency of a disease is an unusual event requiring follow-up, the epidemiologist must compare the observed frequency with the usual or expected frequency of the disease for that population. Since the expected frequency is seldom known, the rate of the disease in the study population must be compared with that in a control or comparison group. The control group can be chosen either by matching individuals in the two groups with respect to several key variables, or alternatively, by choosing groups which resemble each other as closely as possible. The choice of the control group is a central issue in any epidemiological study.

To illustrate these epidemiological concepts, suppose there are three persons diagnosed with lung cancer among a group of workers in a 2,4-D manufacturing plant. To determine if these three lung cancers constitute an excess amount of cancer, the rate of the disease must be calculated. If there are few exposed workers in the plant, e.g. 10, then three cancers represent an extremely high rate of cancer, but if there are 10 000 exposed workers in the plant, then the rate of cancer is much lower (3/10 000) than one would expect in the general population. To make a more accurate judgment as to whether the rates are truly unusual, an appropriate control group must be used for comparison.

The rates of disease occurring in exposed groups are often compared with rates in the general population, which is not always a suitable reference group because of a phenomenon known as the "healthy worker effect", i.e. persons employed are generally in good health, while the general population is composed of persons in poor health as well as in good health. The "healthy worker effect" is an example of a confounding bias because good health is associated both with the risk of dying (in this case a lower risk of dying) and with the exposure (in this case a higher chance of being employed). A more compatible comparison group would be workers from a second workplace who were not exposed to the same chemical.

II.1.1.2 Measuring the Association

Once an excess rate of disease in a particular population has been identified, the next step is to look for an association between the adverse health outcome and exposure to an agent suspected of causing the disease. The problem can be examined from two points of view. The persons who have been exposed to the agent can be studied to see if they develop the disease, or the persons who have the disease can be studied to see if they have been exposed to the agent. This situation is summarized in Table II-1, which is known in its simplest form as a 2 x 2 contingency table.

In a 2 x 2 contingency table, data are arranged in a "yes or no" situation both for the exposure (exposed vs nonexposed) and for the outcome (diseased vs not diseased). When convenient, the table can be expanded by subdividing either variable into classes or levels. For example, exposure could be stratified into low, medium and high or by number of years worked.

The epidemiologist will design a study to determine the values for each cell of the 2 x 2 table. Once this is done, an appropriate statistical analysis must be performed in order to determine whether there is an association between the exposure and the adverse health outcome. The purpose of this analysis is to test whether the association is significant. "Significance" in the statistical sense

Table II-1. Two-by-two contingency table.

		DISEASE		
		+	-	
EXPOSURE TO AGENT	+	a	b	a+b
	-	c	d	c+d
		a+c	b+d	a+b+c+d

a = Number of individuals who have been exposed to the agent and have developed the disease.

b = Number of individuals who have been exposed to the agent but have not developed the disease.

c = Individuals who have not been exposed to the agent but have developed the disease.

d = Individuals who have neither had the exposure nor the disease.

a+b = All individuals who have been exposed.

a+c = All individuals with the disease in the population.

b+d = All individuals who have not developed the disease.

c+d = All individuals who have not been exposed.

a+b+c+d = All individuals in the population.

implies that if an association is found, it is unlikely to have occurred by chance (sampling variation) alone. This in turn means that there is a high probability of a true relationship between the chemical and the disease in question.

Statistical significance is highly dependent on numerical values, particularly the number of individuals in the study (sample size). It often does not provide any information as to the clinical or biological importance of the results. Monson (1980) calls statistical significance a test of "stability" of the association. "Biological significance" differs from statistical significance in that it is a "judgment" value based on the biological or clinical importance of the findings. For example, if a disease which is invariably fatal within one month is treated with a new drug and one patient in the treatment group survives versus none in the placebo group (control), this is a biologically, but not necessarily a statistically, significant event.

After an appropriate statistical analysis (e.g. Chi-squared Test) has shown that there is a statistically significant relationship between the suspect cause and the health outcome, the strength or magnitude of the association must be determined. In the case of a 2 x 2 table, this is achieved by comparing the rates of disease of the exposed and nonexposed groups. This comparison is usually made by calculating the ratio (Relative Risk: RR) or the differences (Attributable Risk: AR) of those rates.

The formula for the Relative Risk is as follows (refer to Table II-1):

$$RR = \frac{\frac{a}{a+b}}{\frac{c}{c+d}}$$

The above calculations are valid only when the incidence rates are available for the exposed and nonexposed groups, as in the cohort or incidence studies (see Section II.1.2.2). In a study done retrospectively, the exact population at risk is not known and the choice of the number of cases and controls determines the prevalence of the disease. Therefore, no direct measure of incidence rate (risk) is possible. In this case, the relative risk can be estimated by the ratio of the cross products (i.e. ad/bc), providing the disease is rare. Then, the ratio of the cross products approximates the RR because the value of "c" will be small in comparison to "d" and the value of "a" will be small compared with "b". This estimate is also called the "Odds Ratio" and represents the odds of having a disease among the exposed relative to the odds among the nonexposed.

RR = 1 indicates no relationship, RR > 1 indicates a positive association and RR < 1 indicates negative association. It is generally accepted among epidemiologists that a relative risk between 0.8 and 1 or between 1 and 1.2 indicates that if an association exists within this range it is too weak to be detected by nonexperimental

(observational) epidemiological methods; it does not indicate that RR is equal to 1 (i.e. no relationship).

The Attributable Risk (AR) is the rate of the disease in exposed individuals that can be attributed to the exposure. It is calculated by taking the difference in incidence rates between an exposed group and a nonexposed group. It provides an estimate of how much of the disease could be prevented among the exposed if the suspect agent were eliminated. The formula for the Attributable Risk is as follows (refer to Table II-1):

$$AR = \frac{a}{a+b} - \frac{c}{c+d}$$

Finally, sample size must be considered when assessing the level of statistical significance of positive findings and even more so in the case of no association. When confronted by "no statistically significant association" it is essential to be able to state, with a reasonable degree of confidence, that the study in question had enough "power" to find an effect if there was one. "Power" is the ability to detect the differences (whether in frequencies (rates) or in mean values) which are the object of the study. Only when the study has enough power can a result showing no association be assumed to mean that an association does not exist. This concept stems from the well known Type I and Type II statistical errors. For formulae to calculate sample size, etc., the reader is referred to general textbooks on epidemiology (McMahon and Pugh 1970) and statistics (Smith 1969; Hill 1971).

II.1.1.3 Selecting the Method of Study

There are several kinds of epidemiological studies which are used to assess the association between an agent and an adverse health outcome. Some methodologies are considered to be more valid than others and some researchers believe that the closer the methodology is to the randomized, controlled experiment, the more reliable are the conclusions of the study. However, experimental or intervention studies are rare in occupational epidemiology and most studies are observational in nature.

II.1.2 OBSERVATIONAL STUDIES

There are several different methods of classifying observational study types and a pronounced lack of consensus exists among epidemiologists over which method is the most suitable.

Epidemiological studies are called observational when the allocation of populations into study groups on the basis of exposure is not under the control of the investigator. Differences in the outcome of interest are therefore observed, not created. This contrasts with the case of experimental studies such as clinical trials where the allocation is usually done by random process.

II.1.2.1 Descriptive Studies

This type of study describes the disease under question in terms of person, place and time (Mausner and Bahn 1974). The main purpose of a descriptive study is to provide hypotheses for the occurrence or cause of the disease, i.e. they are indicators of areas to be followed up by analytical studies.

Case Report

The case report or case study, often used to report findings associated with chemical exposure, could be considered to be a type of descriptive study. Usually published in medical journals, they describe the experience of clinicians with a small number of patients who have been involved with a given chemical. Since the population at risk (the denominator) is not known, a rate cannot be derived for a case study; nevertheless, they do suggest possibilities for more controlled studies to follow.

Cross-sectional (prevalence) Studies

The cross-sectional study looks at a disease in a population at one point in time (a+b+c+d in Table II-1). An example of a cross-sectional study is a health survey. The limitation of this type of study is that the time relationship between exposure and the development of the disease can only be assumed. In comparison, a longitudinal (or monitoring) study is one in which a group of exposed individuals are followed over a period of time during which both exposure and health outcomes are monitored.

II.1.2.2 Analytical Studies

Cohort Study

This type of study can be used to determine a possible relationship between exposure and health outcomes. In the cohort study, persons in the study population are followed and investigated. There are two types of cohort studies. In a "prospective cohort" or "concurrent" study, subjects in the exposed and nonexposed groups are observed over a period of time after the investigation has begun. The study group (a+b in Table II-1) has been exposed to the substance of interest and a proportion of them eventually develop a particular health problem. A control group that is not exposed to the suspect agent (c+d in Table II-1) is also followed with respect to the disease of interest. For example, all workers in the asbestos factory who handle asbestos are enrolled in a study and are compared with a similar group of working persons who do not handle asbestos. After an appropriate amount of

time, during which the number of lung cancer victims in each group are identified, a relative risk can be calculated. Prospective cohort studies have a number of disadvantages. Large numbers of persons must be enrolled in the beginning of the study because the risk of developing the disease of interest is relatively low and a significant proportion of persons may be lost to follow-up. They are also expensive and time consuming.

The second type of cohort study is known by many names including "historical prospective", "nonconcurrent", "prospective study done retrospectively" and others. Here the researcher looks at a cohort of persons who became members of a group in the past. For example, one might study all workers at a particular factory who joined the factory in 1950 and then see how many have developed lung cancer by 1980. In order to set up historical cohorts it is necessary to have a good documentation on the exposure experience of the group. Although good employment history records are usually kept by the industries as well as by the unions, these often do not have measures of exposure. This type of study has the advantage of being quick and less expensive and it permits the same analysis as the classical (prospective) cohort, because it still measures the incidence of the disease.

Case-Control Study

In a case-control study, persons with a given disease (cases) (a+c in Table II-1) are matched (individually or by group) in terms of age, sex and other relevant characteristics to non-diseased (control) persons (b+d in Table II-1). Information is then sought on the past exposure of both the cases and the controls to the chemical in question. For example, the cases may be all persons diagnosed with lung cancer in 1980 in one hospital and the controls might be age-and sex-matched patients in the same hospital who were admitted at the same time for motor vehicle accidents. Both groups would then be assessed as to their possible exposure to asbestos. After compiling the necessary information, analysis of the data is done by calculating the odds ratio in the 2 x 2 table.

This type of study has the advantage of being relatively inexpensive to carry out. Results can be obtained quickly and it is particularly well-suited for the study of rare conditions or diseases (such as cancer). The main disadvantage of the case-control study is that it is prone to a number of biases, particularly bias due to recall. In a recent publication, Sackett (1979) catalogued 35 biases that can arise in sampling and measurement in a case-control study. Many of them also arise in other types of studies. A few will be discussed, as they may be pertinent to the studies concerning 2,4-D here reviewed.

First, the criteria for who is a "case" must be precisely defined. Different countries may have different diagnostic criteria or

terminology for the same disease. Therefore, cases of cancer in different studies may not be directly comparable. Second, as we have already mentioned, the controls must be carefully chosen in order to avoid a confounding bias. Third, in many studies there will be a proportion of cases and controls for which no information can be obtained, and this may influence the results. Fourth, the study should be conducted by objective investigators who must not subconsciously seek more information from the cases than from the controls. Finally, there is the above-mentioned "recall" bias: persons afflicted by an illness may be more likely to recall certain events than the control persons, especially when the association between a disease and a factor is well known. For example, it may be that lung cancer cases may recall their working with asbestos better than the motor vehicle accident patients since the link between asbestos and lung cancer is well publicized.

II.1.3 INTERVENTION STUDIES

The randomized intervention study is an experiment. It is often used to evaluate new drugs or to test the effectiveness of a new vaccine. In this type of study, persons meeting eligibility criteria are randomly assigned to receive either an active treatment or a placebo. Although intervention studies are preferred, they are not used very often in epidemiology for economic, political and ethical reasons. Because of the potential health hazards, no randomized intervention studies have been carried out with respect to 2,4-D.

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